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(54) **Benzylidenethiazolidine derivatives, their preparation and their use for the inhibition of lipid peroxides**

Benzylidenthiazolidinderivate, ihre Herstellung und ihre Anwendung als Lipidperoxid-Inhibitoren

Dérivés de benzylidène thiazolidines, leur préparation et leur utilisation pour l'inhibition de peroxydes lipidiques

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(56) References cited:
EP-A- 0 177 353 **EP-A- 0 207 605**
EP-A- 0 257 781 **EP-A- 0 277 836**
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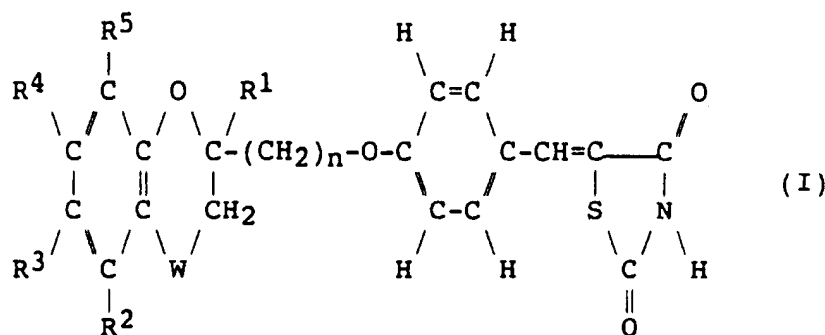
Description

[0001] The present invention relates to a series of novel benzylidenethiazolidine derivatives which have the ability to inhibit the formation of lipid peroxide in the mammalian body, to the use of these compounds for the treatment of arteriosclerosis and other diseases and disorders arising from an imbalance in the lipid peroxide level, to processes for the preparation of these compounds.

[0002] Certain thiazolidinone derivatives having the ability to lower blood lipid and blood glucose levels are disclosed in U.S. Patent No. 4 572 912 and in European Patent No. 207 867. Other thiazolidinone derivatives having a similar type of activity are disclosed in European Patent No. 8203; but such compounds are structurally less similar to those of the present invention. However, the closest prior art of which we are presently aware is US Patent No. 4 873 255, which discloses a series of compounds which differ from those of the present invention in that they are benzylthiazolidine derivatives, rather than the benzylidenethiazolidine derivatives of the present invention.

[0003] We have now discovered a series of novel benzylidenethiazolidine derivatives which not only have the ability to inhibit the activity of lipid peroxide in the mammalian metabolism, but which also are of considerable value in preparing cheaply, effectively and in relatively high yields the compounds of the aforementioned US Patent No. 4 873 255, which are at present thought to be of greater value for their therapeutic activity.

[0004] Thus, the compounds of the present invention may be represented by the formula (I):



in which R¹, R² and R⁵ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

R³ and R⁴ are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; a carboxy group; an alkoxycarbonyl group having from 2 to 7 carbon atoms; an aryloxy carbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; a formyloxy group; an arylcarbonyloxy group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; an alkoxy group having from 1 to 5 carbon atoms; a substituted alkoxy group having from 1 to 5 carbon atoms and substituted by at least one of substituents (b), defined below; or a halogen atom;

W represents a methylene group (>CH₂), a carbonyl group (>C=O) or a group of formula >C=N-OV

wherein V represents: a hydrogen atom; an alkylcarbonyl group having from 2 to 6 carbon atoms; an arylcarbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; an alkyl group having from 1 to 5 carbon atoms; or a substituted alkyl group having from 1 to 5 carbon atoms and substituted by at least one of substituents (d), defined below; and

n is an integer of from 1 to 3;

substituents (a) :

[0005] alkyl groups having from 1 to 5 carbon atoms; alkoxy groups having from 1 to 5 carbon atoms; and halogen atoms;

substituents (b) :

[0006] aryl groups which have from 6 to 10 ring carbon atoms and which are unsubstituted or which are substituted by at least one of substituents (a), defined above; carboxy groups; alkoxycarbonyl groups having from 2 to 6 carbon atoms; and groups of formula -CONR⁶R⁷, where

R⁶ and R⁷ are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 5 carbon atoms; or an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or which is substituted by at least one of substituents (a), defined above; or R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a heterocyclic group which has from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (c), defined below;

substituents (c):

[0007] alkyl groups having from 1 to 5 carbon atoms; and aryl groups which have from 6 to 10 ring carbon atoms and which are unsubstituted or which are substituted by at least one of substituents (a), defined above;

substituents (d):

[0008] carboxy groups and alkoxycarbonyl groups having from 2 to 6 carbon atoms; and pharmaceutically acceptable salts thereof.

[0009] The invention still further provides a pharmaceutical composition for the treatment or prophylaxis of diseases and disorders arising from an imbalance in the lipid peroxide level, said composition comprising an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

[0010] The invention still further provides the use of compounds of formula (I) and pharmaceutically acceptable salts thereof in therapy.

[0011] The invention still further provides the use of compounds of formula (I) and pharmaceutically acceptable salts thereof for the manufacture of a medicament for reducing lipid peroxide levels in an animal, especially a mammal, e. g. a human being.

[0012] The invention still further provides processes for preparing the compounds of the invention and for using the compounds of the invention to prepare benzylthiazolidine derivatives, as described in greater detail hereafter.

[0013] In the compounds of the present invention where R¹, R², R³, R⁴ or R⁵ represents an alkyl group having from 1 to 10 carbon atoms, this may be a straight or branched chain alkyl group, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, hexyl, neohexyl, 1-methylpentyl, 3-methylpentyl, 1,3-dimethylbutyl, 2-ethylbutyl, heptyl, 1-methylhexyl, 1-propylbutyl, 4,4-dimethylpentyl, octyl, 1-methylheptyl, 2-ethylhexyl, 5,5-dimethylhexyl, 1,1,3,3-tetramethylbutyl, nonyl, decyl, 1-methylnonyl, 3,7-dimethyloctyl and 7,7-dimethyloctyl groups. Of these, we prefer that R¹, R², R³, R⁴ and R⁵ should represent a straight or branched chain alkyl group having from 1 to 4 carbon atoms. More preferably, where R¹, R², R³ or R⁵ represents an alkyl group, it is a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group, and most preferably a methyl group. More preferably, where R⁴ represents an alkyl group, it is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl group, and most preferably a methyl or t-butyl group, particularly a methyl group.

[0014] Where R³ and/or R⁴ represents an alkylcarbonyl group, this may be a straight or branched chain alkylcarbonyl group having from 2 to 11 carbon atoms. Examples of such alkylcarbonyl groups include the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 2-methylpentanoyl, heptanoyl, isoheptanoyl, octanoyl, isooctanoyl, nonanoyl, 2-methyloctanoyl, isononanoyl, decanoyl and undecanoyl groups. Preferably, where R³ and/or R⁴ represents an alkylcarbonyl group, this is a straight or branched chain alkylcarbonyl group having from 2 to 7 carbon atoms, more preferably a straight or branched chain alkylcarbonyl group having from 2 to 5 carbon atoms, and most preferably an acetyl group.

[0015] Where R³ and/or R⁴ represents an arylcarbonyl group, whose aryl group has from 6 to 10 carbon atoms and may optionally have one or more substituents, it has, excluding any substituents, a total of from 7 to 11 carbon atoms. Examples of such groups include the benzoyl, 1-naphthoyl and 2-naphthoyl groups, which may be unsubstituted or substituted. Where the aryl moiety is substituted, we prefer that it should have from 1 to 5 substituents on the aromatic

ring. These substituents are selected from substituents (a), and examples of such substituents include:

- (1) straight and branched chain alkyl groups having from 1 to 5 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl and 1-ethylpropyl groups;
- (2) straight and branched chain alkoxy groups having from 1 to 5 carbon atoms, such as the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy and isopentyloxy groups; and
- (3) halogen atoms, such as the chlorine, fluorine and bromine atoms.

[0016] Examples of such groups which may be represented by R^3 and/or R^4 include: (a) the benzoyl, 1-naphthoyl and 2-naphthoyl groups; (b) the 4-methylbenzoyl, 2-propylbenzoyl, 3-butylbenzoyl, 4-pentylbenzoyl, 4-methyl-1-naphthoyl and 4-propyl-2-naphthoyl groups; (c) the 2-methoxybenzoyl, 4-ethoxybenzoyl, 4-butoxybenzoyl, 4-isopentyloxybenzoyl and 4-methoxy-1-naphthoyl groups; and (d) the 3-chlorobenzoyl, 4-fluorobenzoyl, 4-bromobenzoyl and 4-chloro-2-naphthoyl groups. Where R^3 and/or R^4 represents an arylcarbonyl group, this is preferably an arylcarbonyl group having from 7 to 11 carbon atoms whose aryl moiety has no substituents, and is most preferably a benzoyl group.

[0017] Where R^3 and/or R^4 represents an alkoxy carbonyl group, the alkoxy part may be a straight or branched chain group having from 1 to 6 carbon atoms, i.e. the alkoxy carbonyl group has from 2 to 7 carbon atoms. Examples of such alkoxy carbonyl groups include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl, 1-ethylpropoxycarbonyl, hexyloxycarbonyl, neo-hexyloxycarbonyl, 1-methylpentyloxycarbonyl, 3-methylpentyloxycarbonyl, 1,3-dimethylbutoxycarbonyl and 2-ethylbutoxycarbonyl groups. Preferably R^3 represents a straight or branched chain alkoxy carbonyl group having from 2 to 5 carbon atoms and most preferably a methoxycarbonyl, ethoxycarbonyl or t-butoxycarbonyl group. Preferably R^4 represents a straight or branched chain alkoxy carbonyl group having from 2 to 5 carbon atoms.

[0018] Where R^3 and/or R^4 represents an aryloxy carbonyl group, whose aryl part has from 6 to 10 carbon atoms and may optionally have one or more substituents, it has, excluding any substituents, a total of from 7 to 11 carbon atoms. Examples of such groups include the phenoxycarbonyl, 1-naphthyloxy carbonyl and 2-naphthyloxy carbonyl groups, which may be unsubstituted or substituted. Where the aryl moiety is substituted, we prefer that it should have from 1 to 5 substituents on the aromatic ring. These substituents are selected from substituents (a), and examples of such substituents are as given above. Examples of such groups which may be represented by R^3 and/or R^4 include: (a) the phenoxycarbonyl, 1-naphthyloxy carbonyl and 2-naphthyloxy carbonyl groups; (b) the 4-methylphenoxycarbonyl, 2-propylphenoxycarbonyl, 3-butylphenoxycarbonyl, 4-pentylphenoxycarbonyl, 4-methyl-1-naphthyloxy carbonyl and 4-propyl-2-naphthyloxy carbonyl groups; (c) the 2-methoxyphenoxycarbonyl, 4-ethoxyphenoxycarbonyl, 4-butoxyphenoxycarbonyl, 4-isopentyloxyphenoxycarbonyl and 4-methoxy-1-naphthyloxy carbonyl groups; and (d) the 3-chlorophenoxycarbonyl, 4-fluorophenoxycarbonyl, 4-bromophenoxycarbonyl and 4-chloro-2-naphthyloxy carbonyl groups. Where R^3 and/or R^4 represents an aryloxy carbonyl group, this is preferably an aryloxy carbonyl group having from 7 to 11 carbon atoms whose aryl moiety has no substituents, and is most preferably a phenoxycarbonyl group.

[0019] Where R^3 and/or R^4 represents an alkylcarbonyloxy group, the alkyl part may be a straight or branched chain group having from 1 to 10 carbon atoms, i.e. the alkylcarbonyloxy group has from 2 to 11 carbon atoms. Examples of such alkylcarbonyloxy groups include the acetoxyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 2-methylpentanoyl, heptanoyl, isoheptanoyl, octanoyl, isooctanoyl, nonanoyl, 2-methyloctanoyl, isononanoyl, decanoyl and undecanoyl groups. Where R^3 and/or R^4 represents an alkylcarbonyloxy group, this is preferably a straight or branched chain alkylcarbonyloxy group having from 2 to 7 carbon atoms, more preferably a straight or branched chain alkylcarbonyloxy group having from 2 to 5 carbon atoms, and most preferably an acetoxyl group.

[0020] Where R^3 and/or R^4 represents an arylcarbonyloxy group, whose aryl group has from 6 to 10 carbon atoms and may optionally have one or more substituents, it has, excluding any substituents, a total of from 7 to 11 carbon atoms. Examples of such groups include the benzoyloxy, 1-naphthoyloxy and 2-naphthoyloxy groups, which may be unsubstituted or substituted. Where the aryl moiety is substituted, we prefer that it should have from 1 to 5 substituents on the aromatic ring. These substituents are selected from substituents (a), and examples of such substituents are as illustrated above. Examples of such groups which may be represented by R^3 and/or R^4 include: (a) the benzoyloxy, 1-naphthoyloxy and 2-naphthoyloxy groups; (b) the 4-methylbenzoyloxy, 2-propylbenzoyloxy, 3-butylbenzoyloxy, 4-pentylbenzoyloxy, 4-methyl-1-naphthoyloxy and 4-propyl-2-naphthoyloxy groups; (c) the 2-methoxybenzoyloxy, 4-ethoxybenzoyloxy, 4-butoxybenzoyloxy, 4-isopentyloxybenzoyloxy and 4-methoxy-1-naphthoyloxy groups; and (d) the 3-chlorobenzoyloxy, 4-fluorobenzoyloxy, 4-bromobenzoyloxy and 4-chloro-2-naphthoyloxy groups. Where R^3 and/or R^4 represents an arylcarbonyloxy group, this is preferably an arylcarbonyloxy group having from 7 to 11 carbon atoms whose aryl moiety has no substituents, and most preferably a benzoyloxy group.

[0021] Where R^3 and/or R^4 represents an alkoxy group, this may be a straight or branched chain alkoxy group having from 1 to 5 carbon atoms and it may be unsubstituted or it may have one or more substituents selected from substituents (b), defined above and exemplified below. Examples of such groups include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy and isopentyloxy groups, which may be unsubstituted or may be substituted by one or more of substituents (b). Although the number of substituents is, in principle, limited only by the number of substitutable positions and possibly by steric constraints, in practice, we normally prefer from 1 to 3 substituents. Examples of such substituents include:

(1) aryl groups which may be unsubstituted or may have one or more substituents; these may be as defined above in relation to the aryl groups which may be represented by R^3 and R^4 ; examples include the phenyl, 1-naphthyl and 2-naphthyl groups, which may be unsubstituted or may be substituted, preferably with from 1 to 5 substituents, as defined above;

(2) carboxy groups;

(3) alkoxycarbonyl groups having from 2 to 6 carbon atoms, which may be straight or branched chain groups, for example the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl and 1-ethylpropoxycarbonyl groups;

(4) groups of formula $-\text{CONR}^6\text{R}^7$, wherein R^6 and R^7 are the same or different and each represents:

a hydrogen atom,

a straight or branched chain alkyl group having from 1 to 5 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl and 1-ethylpropyl groups,

an aryl group which may be unsubstituted or may be substituted by one or more of substituents (a), defined and exemplified above, and which has from 6 to 10 carbon atoms, such as the phenyl, 1-naphthyl and 2-naphthyl groups and substituted analogues thereof, as exemplified above,

or

R^6 and R^7 , together with the nitrogen atom to which they are attached, may form a heterocyclic ring, as defined and exemplified below.

[0022] The heterocyclic group which may be formed by the $-\text{NR}^6\text{R}^7$ part of the group of formula $-\text{CONR}^6\text{R}^7$ has from 3 to 7 ring atoms and is preferably a saturated group, which may optionally contain an additional oxygen, sulphur or nitrogen atom in the ring. The group may be unsubstituted or it may be substituted by at least one of substituents (c), defined above and exemplified below. In particular, where the heterocyclic group contains an additional nitrogen atom, the nitrogen atom may optionally be substituted; examples of these substituents include:

(i) straight or branched chain alkyl groups having from 1 to 5 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl and 1-ethylpropyl groups, and

(ii) aryl groups which may optionally be substituted by one or more of substituents (a) and which, excluding any substituents, have from 6 to 10 carbon atoms, such as the phenyl, 1-naphthyl and 2-naphthyl group, and such groups having one or more substituents, as defined and exemplified above in relation to R^3 and R^4 .

[0023] Examples of these heterocyclic groups include the 1-pyrrolidinyl, piperidino, morpholino, piperazinyl, N-methylpiperazinyl, N-phenylpiperazinyl, N-(4-methylphenyl)piperazinyl, N-(3-methoxyphenyl)piperazinyl and N-(2-chlorophenyl)piperazinyl groups.

[0024] Examples of the substituted and unsubstituted alkoxy groups which may be represented by R^3 or R^4 include: (a) the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy and isopentyloxy groups, (b) the benzyloxy, phenethyloxy, 3-phenylpropoxy, α -naphthylmethoxy and β -naphthylmethoxy groups, (c) the 4-methylbenzyloxy, 4-butylbenzyloxy, 4-ethylphenethyloxy and 5-methyl- α -naphthylmethoxy groups, (d) the 4-methoxybenzyloxy, 4-ethoxybenzyloxy, 4-butoxyphenethyloxy and 5-methoxy- α -naphthylmethoxy groups, (e) the 4-chlorobenzyloxy, 4-bromobenzyloxy, 4-fluorophenethyloxy and 5-chloro- α -naphthylmethoxy groups, (f) the carboxymethoxy, 2-carboxyethoxy, 3-carboxypropoxy, 3-carboxybutoxy, 3-carboxy-1-methylpropoxy and 1-carboxy-1-methylethoxy

groups, (g) the methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 2-propoxycarbonylethoxy, 3-pentyloxycarbonylpropoxy, 4-butoxycarbonylbutoxy, 3-methoxycarbonyl-1-methylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)-propoxy and 1-(t-butoxycarbonyl)-1-methylethoxy groups, (h) the carbamoylmethoxy, 2-carbamoylethoxy and 4-carbamoylbutoxy groups, (i) the methylaminocarbonylmethoxy, 2-propylaminocarbonylethoxy, 3-(N,N-dimethylaminocarbonyl)propoxy, 4-(N-methyl-N-ethylaminocarbonyl)butoxy and 3-(N,N-dipentylaminocarbonyl)-1-methylpropoxy groups, (j) the phenylaminocarbonylmethoxy, 2-phenylaminocarbonylethoxy, 3-phenylaminocarbonylpropoxy, 4-phenylaminocarbonylbutoxy and 3-phenylaminocarbonyl-1-methylpropoxy groups, (k) the 4-methylphenylaminocarbonylmethoxy and 2-(4-propylphenylaminocarbonyl)ethoxy groups, (l) the 3-(3-ethoxyphenylaminocarbonyl)propoxy and 4-(3-butoxyphenylaminocarbonyl)butoxy groups, (m) the 4-chlorophenylaminocarbonylmethoxy and 3-(4-fluorophenylaminocarbonyl)-1-methylpropoxy groups, (n) the 1-pyrrolidinylcarbonylmethoxy, piperidinocarbonylmethoxy, morpholinocarbonylmethoxy, 2-(piperazinylcarbonyl)ethoxy, 2-(piperidinocarbonyl)ethoxy and 4-(morpholinocarbonyl)butoxy groups, (o) the N-methylpiperazinylcarbonylmethoxy group, (p) the N-phenylpiperazinylcarbonylmethoxy group, (q) the N-(4-methylphenyl)piperazinylcarbonylmethoxy group, (r) the N-(3-methoxyphenyl)piperazinylcarbonylmethoxy group and (s) the N-(2-chlorophenyl)piperazinylcarbonylmethoxy group. Where R³ and/or R⁴ represents an optionally substituted alkoxy group, this is preferably a straight or branched chain alkoxy group having from 1 to 3 carbon atoms, which is unsubstituted or has one or two substituents, the substituents being selected from:

[1] aryl groups having from 6 to 10 carbon atoms and without any substituent on the aromatic ring;

[2] carboxy groups;

[3] straight or branched chain alkoxycarbonyl groups having from 2 to 5 carbon atoms;

[4] carbamoyl groups; and

[5] groups of formula -CONR⁶R⁷ (wherein R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring having from 5 to 7 ring atoms, which may contain an additional oxygen or nitrogen atom in the ring, and which has no substituents.

[0025] R³ more preferably represents a methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-methylethoxy, carbamoylmethoxy, piperidinocarbonylmethoxy or morpholinocarbonylmethoxy group, and most preferably represents a methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group. R⁴ more preferably represents a carboxymethoxy, benzyloxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy or 1-(t-butoxycarbonyl)-1-methylethoxy group, and most preferably a carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group.

[0026] Where R³ and/or R⁴ represents a halogen atom, this may preferably be a chlorine, fluorine or bromine atom. In this case, R³ and/or R⁴ preferably represents a chlorine or fluorine atom, and most preferably a fluorine atom.

[0027] Where V represents an alkylcarbonyl group, this may be a straight or branched chain alkylcarbonyl group having from 2 to 6 carbon atoms such as, for example, an acetyl, propionyl, butyryl or hexanoyl group. In this case, V preferably represents a straight or branched chain alkylcarbonyl group having from 2 to 4 carbon atoms, and most preferably an acetyl group.

[0028] Where V represents an arylcarbonyl group, it may be an arylcarbonyl group having from 7 to 11 carbon atoms, i.e. the aryl group itself (without substituents) has from 6 to 10 carbon atoms, and examples include the benzoyl, 1-naphthoyl and 2-naphthoyl groups. Such groups may be substituted or unsubstituted and, if substituted, may have one or more, preferably from 1 to 5, of substituents (a), as defined and exemplified above. Examples of such groups which may be represented by V include: (a) the benzoyl, 1-naphthoyl and 2-naphthoyl groups; (b) the 4-methylbenzoyl, 2-propylbenzoyl, 3-butylbenzoyl, 4-pentylbenzoyl, 4-methyl-1-naphthoyl and 4-propyl-2-naphthoyl groups; (c) the 2-methoxybenzoyl, 4-ethoxybenzoyl, 4-butoxybenzoyl, 4-isopentyloxybenzoyl and 4-methoxy-1-naphthoyl groups; and (d) the 3-chlorobenzoyl, 4-fluorobenzoyl, 4-bromobenzoyl and 4-chloro-2-naphthoyl groups. Where V represents an arylcarbonyl group, this is more preferably an arylcarbonyl group having from 7 to 11 carbon atoms whose aryl moiety has no substituents, and most preferably a benzoyl group.

[0029] Where V represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 5 carbon atoms and optionally substituted by one or more of substituents (d). Although there is no particular limitation on the number of substituents on the alkyl group, from one to three substituents are preferred. Examples of the unsubstituted groups include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, ne-

opentyl, 2-methylbutyl and 1-ethylpropyl groups. The substituted group may be any of these unsubstituted groups but substituted by one or more of substituents (d). Examples of the substituents include:

(1) carboxy groups; and

(2) straight and branched chain alkoxy carbonyl groups having from 2 to 6 carbon atoms such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl and 1-ethylpropoxycarbonyl groups.

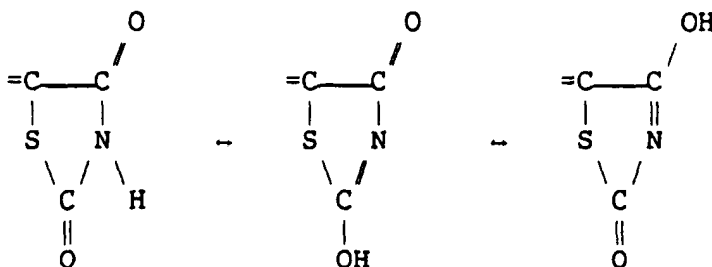
[0030] Examples of such substituted and unsubstituted groups which may be represented by V include: (a) the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl and 1-ethylpropyl groups, (b) the carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, 3-carboxybutyl, 3-carboxy-1-methylpropyl and 1-carboxy-1-methylethyl groups, and (c) the methoxycarbonylmethyl, 3-methoxycarbonylpropyl, ethoxycarbonylmethyl, 3-ethoxycarbonylpropyl, 2-propoxycarbonylethyl, 3-pentyloxycarbonylpropyl, 4-butoxycarbonylbutyl, 3-methoxycarbonyl-1-methylpropyl, 1-methoxycarbonyl-1-methylethyl, t-butoxycarbonylmethyl, 3-(t-butoxycarbonyl)propyl and 1-(t-butoxycarbonyl)-1-methylethyl groups.

[0031] The symbol n represents an integer of from 1 to 3, and is preferably 1 or 2, and most preferably 1.

[0032] The compounds of the present invention can form salts with bases. There is no particular restriction on the nature of these salts, provided that, where they are intended for therapeutic use, they are pharmaceutically acceptable. Where they are intended for non-therapeutic uses, e.g. as intermediates in the preparation of other, and possibly more active, compounds, even this restriction does not apply. Examples of such salts include: salts with an alkali metal, such as sodium, potassium or lithium; salts with an alkaline earth metal, such as barium or calcium; salts with another metal, such as magnesium or aluminium; organic base salts, such as a salt with dicyclohexylamine; and salts with a basic amino acid, such as lysine or arginine. Depending on the nature of the substituent groups, the compounds of the present invention may contain one or more, e.g. one, two or three carboxy groups, and, accordingly, where the cation is monobasic, the salts may be a mono-, di- or tri- salt. Pharmaceutically acceptable salts are preferred.

[0033] The compounds of the present invention have an asymmetric carbon atom at the 2-position of the chroman ring and can thus form optical isomers. They also have a double bond in the benzylidene moiety and can therefore form geometrical isomers. Moreover, certain of the substituent groups may contain one or more asymmetric carbon atoms in their molecules, and can thus form optical isomers. Although these are all represented herein by a single molecular formula, the present invention includes both the individual, isolated isomers and mixtures, including racemates thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques. In the process, method and composition of the invention, the individual isomers or a mixture of isomers may be used.

[0034] In addition, all of the compounds of the present invention may exist in the form of tautomers, as represented below [in which, for the sake of clarity, only the thiazolidinedione or equivalent part of the molecule is shown, the remainder being as in formula (I)]:



[0035] Each of these tautomers individually forms a part of this invention, although all are represented herein by a single formula, and, in practice, any specific compound may normally be expected to be a mixture of all tautomers.

[0036] The preferred compounds of the present invention are those compounds of formula (I) and salts thereof in which:

- (i) R¹ represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 10 carbon atoms.
- (ii) R² represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 10 carbon atoms.
- 5 (iii) R³ and R⁴ are the same or different and each represents:
- (A) a hydrogen atom;
- (B) a straight or branched chain alkyl group having from 1 to 10 carbon atoms;
- 10 (C) a formyl group;
- (D) a straight or branched chain alkylcarbonyl group having from 2 to 11 carbon atoms;
- 15 (E) an arylcarbonyl group having from 7 to 11 carbon atoms which is unsubstituted or has from one to five substituents, the substituents being selected from
- (1) alkyl groups having from 1 to 5 carbon atoms,
- (2) alkoxy groups having from 1 to 5 carbon atoms and (3) halogen atoms;
- 20 (F) a carboxy group;
- (G) a straight or branched chain alkoxycarbonyl group having from 2 to 7 carbon atoms;
- 25 (H) an aryloxycarbonyl group having from 7 to 11 carbon atoms;
- (I) a hydroxy group;
- (J) a straight or branched chain alkylcarbonyloxy group having from 2 to 11 carbon atoms;
- 30 (K) an arylcarbonyloxy group having from 7 to 11 carbon atoms, whose aryl moiety is unsubstituted or has from one to five substituents, the substituents being selected from
- (1) straight or branched chain alkyl groups having from 1 to 5 carbon atoms,
- 35 (2) straight or branched chain alkoxy groups having from 1 to 5 carbon atoms and
- (3) halogen atoms;
- (L) a straight or branched chain alkoxy group having from 1 to 5 carbon atoms which is unsubstituted or has from one to three substituents, the substituents being selected from
- 40 (1) aryl groups having from 6 to 10 carbon atoms which themselves are unsubstituted or have from one to five substituents on the aromatic ring, the substituents being selected from (a) straight or branched chain alkyl groups having from 1 to 5 carbon atoms, (b) straight or branched chain alkoxy groups having from 1 to 5 carbon atoms and (c) halogen atoms,
- 45 (2) carboxy groups,
- (3) straight or branched chain alkoxycarbonyl groups having from 2 to 6 carbon atoms,
- (4) groups of formula -CONR⁶R⁷, wherein R⁶ and R⁷ are the same or different and each represents
- [1] a hydrogen atom,
- 50 [2] a straight or branched chain alkyl group having from 1 to 5 carbon atoms,
- [3] an aryl group having from 6 to 10 carbon atoms which is unsubstituted or has from one to five substituents on the aromatic ring, the substituents being selected from (i) straight or branched chain alkyl groups having from 1 to 5 carbon atoms, (ii) straight or branched chain alkoxy groups having from 1 to 5 carbon atoms and (iii) halogen atoms, or
- 55 [4] R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted or being substituted by at least one substituent, the substituent being selected from (i) straight or branched chain alkyl groups having from 1 to 5 carbon

atoms and (ii) aryl groups having from 6 to 10 carbon atoms, which themselves are unsubstituted or are substituted by from 1 to 5 substituents, the substituents being selected from (a) straight or branched chain alkyl groups having from 1 to 5 carbon atoms, (b) straight or branched chain alkoxy groups having from 1 to 5 carbon atoms and (c) halogen atoms; or

(M) a halogen atom.

(iv) R⁵ represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 10 carbon atoms.

(v) W represents a methylene group, a carbonyl group, or a group of formula >C=N-OV, wherein V represents:

(1) a hydrogen atom,

(2) a straight or branched chain alkylcarbonyl group having from 2 to 6 carbon atoms,

(3) an arylcarbonyl group having from 7 to 11 carbon atoms, or

(4) a straight or branched chain alkyl group having from 1 to 5 carbon atoms, said group being unsubstituted or being substituted by from one to three substituents, the substituents being selected from

[1] carboxy groups and

[2] straight or branched chain alkoxy carbonyl groups having from 2 to 6 carbon atoms.

(vi) n is 1 or 2.

[0037] In particular, of these, we prefer those compounds of formula (I) in which R¹ is as defined in (i) above; R² is as defined in (ii) above; R³ and R⁴ are as defined in (iii) above; R⁵ is as defined in (iv) above; W is as defined in (v) above; and n is as defined in (vi) above.

[0038] The more preferred compounds of the present invention are those compounds of formula (I) in which:

(vii) R¹ represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 4 carbon atoms.

(viii) R² represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 4 carbon atoms.

(ix) R³ and R⁴ are the same or different and each represents:

(A) a hydrogen atom;

(B) a straight or branched chain alkyl group having from 1 to 4 carbon atoms;

(C) a straight or branched chain alkylcarbonyl group having from 2 to 7 carbon atoms;

(D) an arylcarbonyl group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted;

(E) a carboxy group;

(F) a straight or branched chain alkoxy carbonyl group having from 2 to 5 carbon atoms;

(G) a hydroxy group;

(H) a straight or branched chain alkylcarbonyloxy group having from 2 to 7 carbon atoms;

(I) an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted;

(J) a straight or branched chain alkoxy group having from 1 to 3 carbon atoms, said group being unsubstituted or being substituted by one or two substituents, the substituents being selected from

[1] aryl groups having from 6 to 10 carbon atoms and whose aryl moiety is unsubstituted,

[2] carboxy groups,

[3] straight or branched chain alkoxy carbonyl groups having from 2 to 5 carbon atoms,

[4] carbamoyl groups, and

[5] groups of formula $-\text{CONR}^6\text{R}^7$, wherein R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted; and

5 (K) halogen atoms.

(x) R^5 represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 4 carbon atoms;

10 (xi) W represents a methylene group or a group of formula $>\text{C}=\text{N}-\text{OV}$
wherein V represents:

- (1) a hydrogen atom,
- (2) a straight or branched chain alkylcarbonyl group having from 2 to 4 carbon atoms, or
- (3) a benzoyl group.

15 [0039] In particular, of these, we prefer those compounds of formula (I) and salts thereof in which R^1 is as defined in (vii) above, R^2 is as defined in (viii) above, R^3 and R^4 are as defined in (ix) above, R^5 is as defined in (x) above, W is as defined in (xi) above, and n is as defined in (vi) above.

20 [0040] Still more preferred compounds of the present invention of the general formula (I) are those in which:

(xii) R^1 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

(xiii) R^2 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

25 (xiv) R^3 represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group, a straight or branched chain alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a carboxy group, a straight or branched chain alkoxy carbonyl group having from 2 to 5 carbon atoms, a hydroxy group, a straight or branched chain alkylcarbonyloxy group having from 2 to 5 carbon atoms, a benzoyloxy, methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-methylethoxy, carbamoylmethoxy, piperidinocarbonylmethoxy or morpholinocarbonylmethoxy group, or a chlorine or fluorine atom.

35 (xv) R^4 represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl group, a straight or branched chain alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a hydroxy group, a straight or branched chain alkylcarbonyloxy group having from 2 to 5 carbon atoms, an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted, a carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy or 1-(t-butoxycarbonyl)-1-methylethoxy group, or a chlorine or fluorine atom.

40 (xvi) R^5 represents a hydrogen atom, or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

45 (xvii) W represents a methylene group or a group of formula $>\text{C}=\text{N}-\text{OV}$, wherein V represents a hydrogen atom or an acetyl group.

[0041] In particular, of these, we prefer those compounds of formula (I) and salts thereof in which R^1 is as defined in (xii) above, R^2 is as defined in (xiii) above, R^3 is as defined in (xiv) above, R^4 is as defined in (xv) above, R^5 is as defined in (xvi) above, W is as defined in (xvii) above, and n is as defined in (vi) above.

50 [0042] The most preferred compounds of the present invention are those compounds of formula (I) in which:

(xviii) R^1 represents a methyl group.

(xix) R^2 represents a hydrogen atom or a methyl group.

55 (xx) R^3 represents a hydrogen atom, a methyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, hydroxy, acetoxymethoxy, methoxy, benzyloxy, carboxymethoxy or 3-carboxypropoxy group, or a fluorine atom;

(xxi) R^4 represents a hydrogen atom, a methyl, t-butyl, acetyl, hydroxy, acetoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group or a fluorine atom;

(xxii) R^5 represents a hydrogen atom or a methyl group.

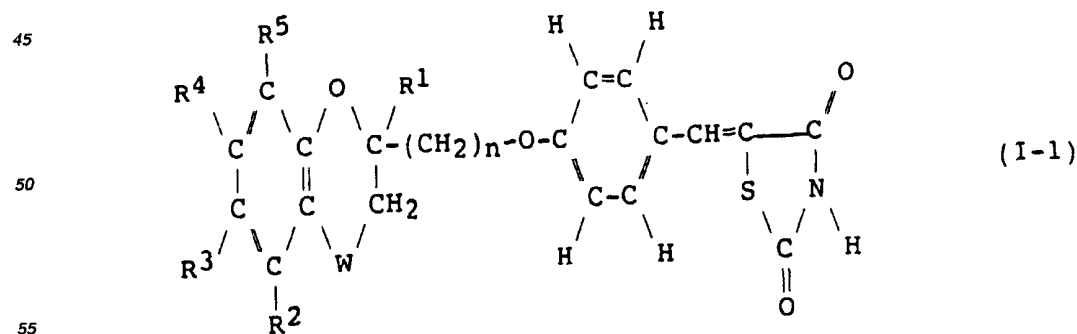
(xxiii) W represents a methylene group.

(xxiv) n is 1.

[0043] In particular, of these, we prefer those compounds of formula (I) and salts thereof in which R^1 is as defined in (xviii) above, R^2 is as defined in (xix) above, R^3 is as defined in (xx) above, R^4 is as defined in (xxi) above, R^5 is as defined in (xxii) above, W is as defined in (xxiii) above, and n is as defined in (xxiv) above.

[0044] Specific examples of compounds of the present invention are shown by the following formulae (I-1) and (I-2), in which the substituent groups are as defined by the corresponding one of Tables 1 and 2, i.e. formula (I-1) relates to Table 1 and formula (I-2) relates to Table 2. In the Tables, the following abbreviations are used:

Ac	acetyl
Boz	benzoyl
Bu	butyl
iBu	isobutyl
tBu	t-butyl
iByr	isobutyryl
Bz	benzyl
Car	carbamoyl
Dc	decyl
Et	ethyl
Fo	formyl
Me	methyl
Mec	methoxycarbonyl
Mor	morpholino
Npo	naphthoyl
Oc	octyl
Ph	phenyl
Pip	piperidyl
Piv	pivaloyl
Pr	propyl
Pm	propionyl
Pyrd	pyrrolidinyl
Tmb	1,1,3,3-tetramethylbutyl
Va	valeryl



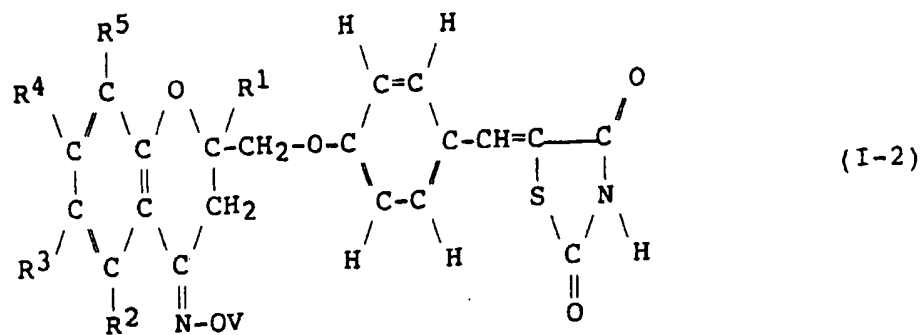


Table 1

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Cpd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	W	<u>n</u>
1-1	H	H	H	H	H	CH ₂	1
1-2	Me	H	H	H	H	CH ₂	1
1-3	Me	H	H	H	H	CH ₂	2
1-4	Me	H	F	H	H	CH ₂	1
1-5	Me	H	Cl	H	H	CH ₂	1
1-6	Me	H	H	F	H	CH ₂	1
1-7	Me	Me	H	Me	H	CH ₂	1
1-8	Me	Me	Me	Me	Me	CH ₂	1
1-9	Me	H	H	HO	Me	CH ₂	1
1-10	Me	H	H	HO	Me	CH ₂	2
1-11	Me	H	H	HOOCCH ₂ O	Me	CH ₂	1
1-12	Me	H	H	HOOCCH ₂ O	Me	CO	1
1-13	Me	H	H	AcO	Me	CH ₂	1
1-14	Me	H	H	AcO	Me	CO	1
1-15	Me	H	H	BozO	Me	CH ₂	1
1-16	Me	H	H	BozO	Me	CO	1
1-17	Me	H	H	3-HOOC-PrO	Me	CH ₂	1
1-18	Me	H	H	3-EtOOC-PrO	Me	CH ₂	1
1-19	Me	H	H	HOOC-C(Me) ₂ -O-	Me	CH ₂	1
1-20	Me	H	H	Mec-C(Me) ₂ -O-	Me	CH ₂	1
1-21	Me	H	H	Car-CH ₂ O-	Me	CH ₂	1
1-22	Me	H	H	diMeCar-CH ₂ O-	Me	CH ₂	1
1-23	Me	H	H	1-Pyrd-CO-CH ₂ O-	Me	CH ₂	1
1-24	Me	H	H	3-(1-Pip-CO)PrO-	Me	CH ₂	1
1-25	Me	H	H	3-(Mor-CO)PrO-	Me	CH ₂	1
1-26	Me	H	HO	H	H	CH ₂	1
1-27	Me	Me	HO	Me	Me	CH ₂	1
1-28	Me	Me	HO	Me	Me	CH ₂	2
1-29	Me	Me	HO	Me	Me	CO	1
1-30	Me	H	HO	tBu	H	CH ₂	1
1-31	Me	H	HO	Tmb	H	CH ₂	1
1-32	tBu	Me	HO	Me	Me	CH ₂	1

Table 1 (continued)

Cpd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	W	n
1-33	iBu	Me	HO	Me	Me	CO	1
1-34	OC	Me	HO	Me	Me	CH ₂	1
1-35	Dc	Me	HO	Me	Me	CH ₂	1
1-36	3,7-diMeOC	Me	HO	Me	Me	CH ₂	1
1-37	Me	Me	AcO	Me	Me	CH ₂	1
1-38	Me	Me	AcO	Me	Me	CO	1
1-39	Me	Me	BozO	Me	Me	CH ₂	1
1-40	Me	Me	MeO	Me	Me	CH ₂	1
1-41	Me	Me	BzO	Me	Me	CH ₂	1
1-42	Me	Me	PrO	Me	Me	CH ₂	1
1-43	H	H	HOOCCH ₂ O	H	H	CH ₂	1
1-44	Me	H	HOOC(CH ₂) ₃ O	tBu	H	CH ₂	1
1-45	Me	Me	HOOCCH ₂ O	Me	Me	CH ₂	1
1-46	Me	Me	HOOCCH ₂ O	Me	Me	CO	1
1-47	Me	Me	EtOOCCH ₂ O	Me	Me	CH ₂	1
1-48	Me	Me	HOOC(CH ₂) ₃ O	Me	Me	CH ₂	1
1-49	Me	Me	HOOC(CH ₂) ₃ O	Me	Me	CH ₂	2
1-50	Me	Me	EtOOC(CH ₂) ₃ O	Me	Me	CH ₂	1
1-51	Me	Me	tBuOOC(CH ₂) ₃ O	Me	Me	CH ₂	1
1-52	Me	Me	HOOC(Me) ₂ O	Me	Me	CH ₂	1
1-53	Me	Me	EtOOC(Me) ₂ O	Me	Me	CH ₂	1
1-54	Me	Me	tBuOOC(Me) ₂ O	Me	Me	CH ₂	1
1-55	H	H	CarCH ₂ O	Me	H	CH ₂	1
1-56	Me	Me	CarCH ₂ O	Me	Me	CH ₂	1
1-57	Me	Me	CarCH ₂ O	Me	Me	CH ₂	2
1-58	Me	Me	CarCH ₂ O	Me	Me	CO	1
1-59	Me	Me	diMeCarCH ₂ O	Me	Me	CH ₂	1
1-60	Me	Me	1-Pyrd-CO-CH ₂ O-	Me	Me	CH ₂	1
1-61	Me	Me	1-Pip-CO-CH ₂ O-	Me	Me	CH ₂	1
1-62	Me	Me	Mor-CO-CH ₂ O-	Me	Me	CH ₂	1
1-63	Me	Me	Mor-CO-CH ₂ O-	Me	Me	CO	1
1-64	Me	Me	Car(CH ₂) ₃ O-	Me	Me	CH ₂	1
1-65	Me	Me	N-EtCar(CH ₂) ₃ O-	Me	Me	CH ₂	1
1-66	Me	Me	N-Bu-N-MeCar(CH ₂) ₃ O-	Me	Me	CH ₂	1
1-67	Me	Me	Mor-CO-(CH ₂) ₃ O-	Me	Me	CH ₂	1
1-68	Me	Me	CarC(Me) ₂ O-	Me	Me	CH ₂	1
1-69	Me	Me	1-Pyrd-CO-C(Me) ₂ O-	Me	Me	CH ₂	1
1-70	Me	H	HOOC-	H	H	CH ₂	1
1-71	Me	H	EtOOC-	H	H	CH ₂	1
1-72	Me	H	tBuOOC-	H	H	CH ₂	1
1-73	Me	H	PhOOC-	HOOC-	H	CH ₂	1
1-74	Me	H	H	HOOC-	H	CH ₂	1
1-75	Me	Me	Fo	Me	Me	CH ₂	1
1-76	Me	H	Ac	HO	Me	CH ₂	1
1-77	Me	H	Ac	HO	Me	CO	1
1-78	Me	H	Prn	HO	Me	CH ₂	1
1-79	Me	H	iByr	HO	Me	CH ₂	1
1-80	Me	H	Piv	HO	Me	CH ₂	1
1-81	Me	H	Boz	HO	Me	CH ₂	1
1-82	Me	H	1-Npo	HO	Me	CH ₂	1

Table 1 (continued)

Cpd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	W	n
1-83	Me	H	Ac	AcO	Me	CH ₂	1
1-84	Me	H	Ac	BozO	Me	CH ₂	1
1-85	Me	H	Ac	1-NpoO	Me	CH ₂	1
1-86	Me	H	Boz	AcO	Me	CH ₂	1
1-87	Me	H	p-MeBoz	PrnO	Me	CH ₂	1
1-88	Me	H	m-ClBoz	HO	Me	CH ₂	1
1-89	Me	H	o-MeOBoz	HO	Me	CH ₂	1
1-90	Me	H	HO	Ac	H	CH ₂	1
1-91	Me	H	HO	Ac	H	CO	1
1-92	Me	H	HO	Boz	H	CH ₂	1
1-93	Me	H	AcO	Ac	H	CH ₂	1
1-94	Me	H	BozO	Ac	H	CH ₂	1
1-95	Me	H	HOOCCH ₂ O-	Ac	H	CH ₂	1
1-96	Me	H	HOOC(CH ₂) ₃ O-	Ac	H	CH ₂	1
1-97	Me	H	HOCC(Me) ₂ O-	Ac	H	CH ₂	1
1-98	Me	Me	tBuOCC(Me) ₂ O-	Me	Me	CH ₂	1

Table 2

Cpd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	V
2-1	H	H	H	H	H	H
2-2	Me	H	H	H	H	H
2-3	Me	Me	Me	Me	Me	H
2-4	Me	H	Cl	H	H	H
2-5	Me	Me	HO	Me	Me	H
2-6	Me	Me	HO	Me	Me	Ac
2-7	Me	Me	HO	Me	Me	Va
2-8	Me	H	HO	tBu	H	Boz
2-9	Me	Me	AcO	Me	Me	Me
2-10	Me	Me	PrO	Me	Me	Pr
2-11	Me	Me	HO	Me	Me	HOOCCH ₂ -
2-12	Me	Me	HO	Me	Me	MeOOCCH ₂ -
2-13	Et	H	BozO	Me	Me	MeOOCCH ₂ -
2-14	Me	Me	HO	Me	Me	EtOOCCH ₂ -
2-15	Me	Me	HO	Me	Me	tBuOOCCH ₂ -
2-16	Me	Me	HO	Me	Me	HOOC(CH ₂) ₃ -
2-17	Bu	H	MeO	Tmb	H	MeOOC(CH ₂) ₃ -
2-18	Me	Me	HO	Me	Me	EtOOC(CH ₂) ₃ -
2-19	Me	Me	HO	Me	H	tBuOOC(CH ₂) ₃ -
2-20	Me	Me	HOOCCH ₂ O-	Me	Me	HOOC(CH ₂) ₃ -
2-21	Me	Me	HOOC(CH ₂) ₃ O-	Me	Me	HOOC(CH ₂) ₃ -
2-22	Me	Me	HOCC(Me) ₂ O-	Me	Me	HOCC(Me) ₂ -
2-23	Me	H	H	HO	Me	H
2-24	Me	H	H	AcO	Me	Ac
2-25	Me	H	H	BozO	Me	Boz
2-26	Me	H	H	HOOCCH ₂ O-	Me	HOOCCH ₂ -
2-27	Me	H	H	EtOOCCH ₂ O-	Me	EtOOCCH ₂ -
2-28	Me	H	H	HOOC(CH ₂) ₃ O-	Me	HOOC(CH ₂) ₃ -
2-29	Me	H	H	MeOOC(CH ₂) ₃ O-	Me	MeOOC(CH ₂) ₃ -

Table 2 (continued)

Cpd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	V
2-30	Me	H	H	HOCC(Me) ₂ O-	Me	HOCC(Me) ₂ -
2-31	Me	H	H	<i>t</i> BuOCC(Me) ₂ O-	Me	<i>t</i> BuOCC(Me) ₂ -

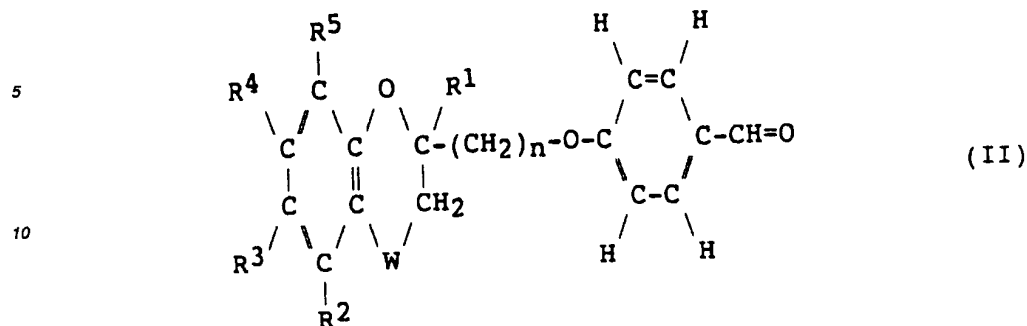
[0045] Of the compounds listed above, the following are particularly preferred, that is to say Compounds No. 1-2, 1-4, 1-7, 1-8, 1-9, 1-11, 1-12, 1-27, 1-30, 1-32, 1-33, 1-36, 1-37, 1-41, 1-45, 1-48, 1-52, 1-56, 1-61, 1-62, 1-70, 1-76 and 2-5. Compounds No.:

- 1-2. 5-[4-(2-Methylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-7. 5-[4-(2,5,7-Trimethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;
- 1-8. 5-[4-(2,5,6,7,8-Pentamethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;
- 1-9. 5-[4-(7-Hydroxy-2,8-dimethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;
- 1-27. 5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-37. 5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-41. 5-[4-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-45. 5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-48. 5-[4-(6-(3-Carboxypropoxy)-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-52. 5-[4-(6-(1-Carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-56. 5-[4-(6-Carbamoylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-61. 5-[4-(6-(Piperidinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 1-62. 5-[4-(6-(Morpholinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione; and
- 1-70. 5-[4-(6-Carboxy-2-methylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;

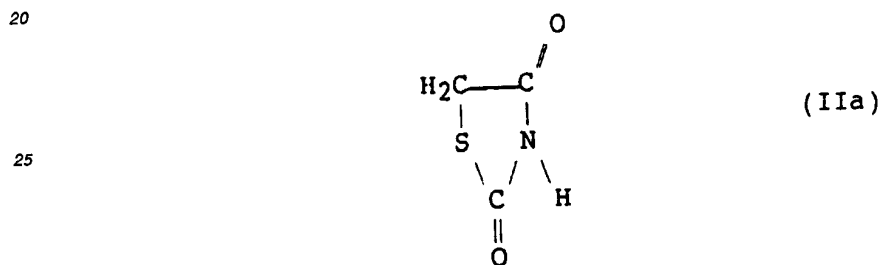
and salts thereof being more preferred.

[0046] The most preferred compounds are Compounds No. 1-27, 1-37 and 1-41 and salts thereof.

[0047] The benzylidenethiazolidine compounds of the present invention can be prepared by a variety of methods well known in the art for the preparation of compounds of this type. Thus, in general terms, the compounds of formula (I) may be prepared by reacting a compound of formula (II):



(in which R¹, R², R³, R⁴, R⁵, n and W are as defined above) with thiazolidine-2,4-dione, which may be represented by the formula (IIa):



[0048] The compound of formula (II), in turn, may be prepared by a variety of methods, and the overall sequence of reactions employed in the preparation of the compounds of the present invention may be illustrated by the following reaction scheme:

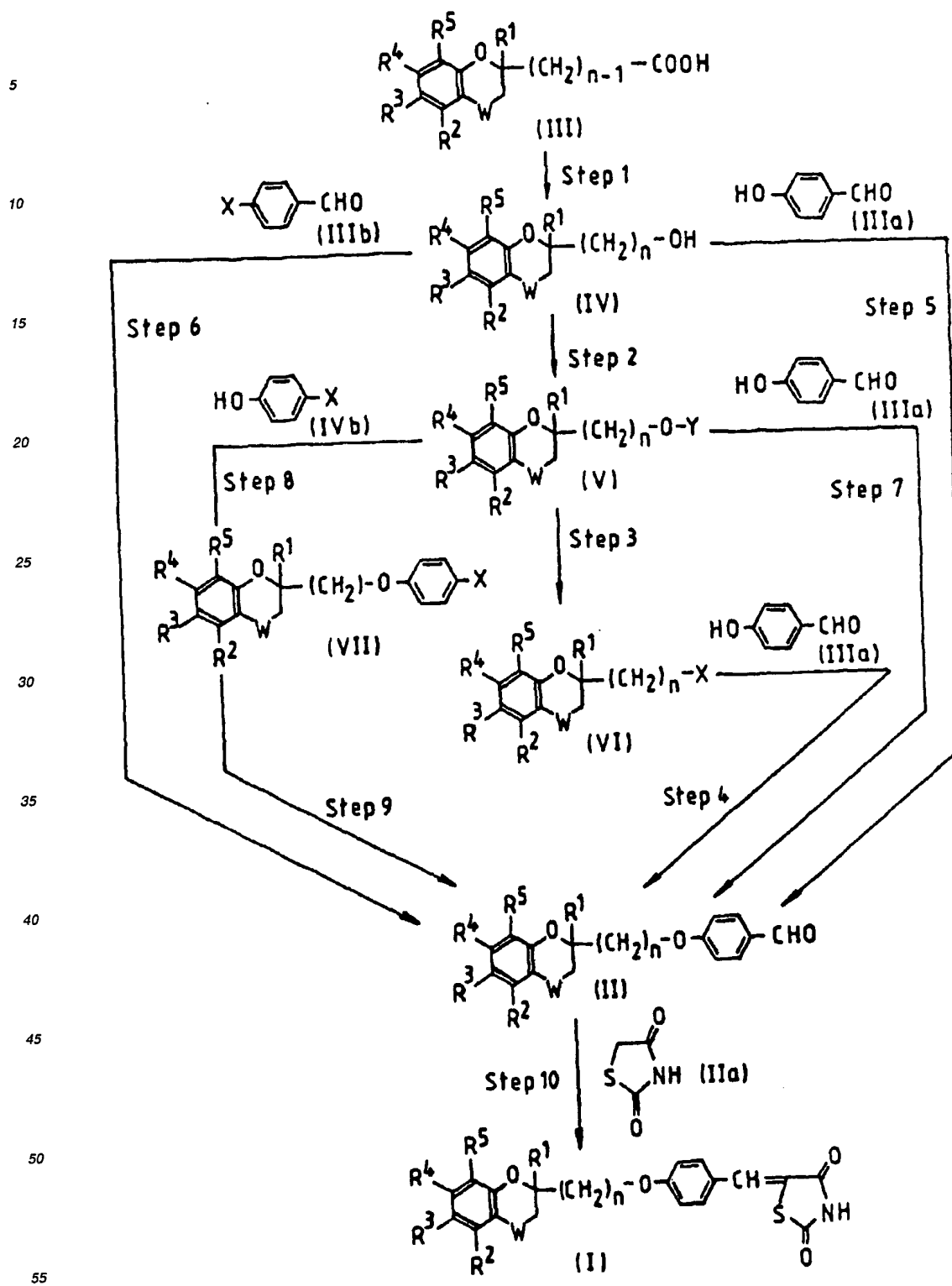
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[0049] In the above formulae, R^1 , R^2 , R^3 , R^4 , R^5 , W and n are as defined above; X represents a halogen atom; and Y represents an alkylsulphonyl or arylsulphonyl group, as further defined and exemplified hereafter.

[0050] In Step 1 of the above reaction scheme, a compound of formula (IV) is prepared by reducing a compound of formula (III) [which may have been prepared, for example, as described in the Journal of the American Oil Chemists' Society, 51, 200 (1974); or Japanese Patent Provisional Publication Tokkai No. Sho 60-51189] using a suitable procedure, for example as described in Japanese Patent Provisional Publication Tokkai No. Sho 60-51189. In this procedure, the reduction is effected using a reducing agent such as lithium aluminium hydride or sodium bis[2-methoxyethoxy] aluminium hydride (trade name: Vitride). The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran and ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene and xylene; aliphatic hydrocarbons, such as hexane, heptane, cyclohexane, petroleum ether, ligroin and ethylcyclohexane. There is no particular limitation upon the amount of reducing agent employed, but a slight excess of the reducing agent over the amount of the compound of formula (III) is preferred. It is more preferred to use from 1 to 2 moles of the reducing agent per mole of the compound of formula (III). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 10°C to 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvents employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 10 or more hours will usually suffice.

[0051] In Step 2 of the above reaction scheme, a compound of formula (V) is prepared by sulphonylation of the compound of formula (IV). This may be carried out by known techniques, for example as described in Japanese Patent Provisional Publication Tokkai No. Sho 63-139182. Thus, the compound of formula (IV) is subjected to sulphonylation, for example using a sulphonyl halide of formula $Y-X$, where Y represents an alkylsulphonyl, propylsulphonyl, butylsulphonyl or pentylsulphonyl group or an arylsulphonyl group in which the aryl part is as defined and exemplified above in relation to the aryl groups included within substituents (b) (especially a phenyl group or a *p*-tolyl group), and X represents a halogen atom (e.g. a chlorine, fluorine, bromine or iodine atom). Examples of such sulphonylating agents include: alkylsulphonyl halides, such as methylsulphonyl chloride, ethylsulphonyl chloride and propylsulphonyl bromide; and arylsulphonyl halides, such as phenylsulphonyl chloride, *p*-tolylsulphonyl chloride and *p*-tolylsulphonyl bromide. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated aliphatic hydrocarbons, such as methylene chloride, 1,2-dichloroethane, chloroform and carbon tetrachloride; ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran and ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene and xylene; water; esters, such as ethyl acetate; amides, especially fatty acid amides, such as dimethylformamide; and mixtures of any two or more of these solvents. The reaction is normally and preferably carried out in the presence of an inorganic base, such as an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide) or an alkali metal carbonate (e.g. potassium carbonate or sodium carbonate); or an organic base, such as an alkylamine (e.g. triethylamine) or a heterocyclic amine (e.g. morpholine, *N*-ethylpiperidine or pyridine). There is no particular limitation on the ratio of the sulphonyl halide to the compound of formula (IV), but a slight excess of sulphonyl halide is preferred. It is more preferred to use from 1 to 2 moles, most preferably from 1.0 to 1.5 moles, of the sulphonyl halide per mole of the compound of formula (IV). The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature in the range of from 10 to 100°C, more preferably from 10 to 50°C. The time required for the reaction may likewise vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, in most cases, a period of from a few hours to 10 or more hours will normally suffice.

[0052] In Step 3 of the above reaction scheme, a compound of formula (VI) is prepared by reacting the compound of formula (V) prepared in Step 2 with an alkali metal halide. Examples of alkali metal halides which may be used in this reaction include sodium iodide, sodium bromide and potassium iodide. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated aliphatic hydrocarbons, such as methylene chloride, 1,2-dichloroethane, chloroform and carbon tetrachloride; ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran and ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene and xylene; and amides, especially fatty acid amides, such as dimethylformamide. The reaction is preferably carried out by reacting the compound of formula (V) with sodium iodide in the presence of dimethylformamide. There is no particular limitation upon the ratio of the alkali metal halide to the compound of formula (V), but the reaction is most preferably

carried out using from 5 to 30 moles, more preferably from 10 to 20 moles, of the alkali metal halide per mole of the compound of formula (V). The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature in the range of from 100 to 200°C, more preferably from 130 to 180°C. The time required for the reaction may likewise vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, in most cases, a period of from a few hours to 10 or more hours will normally suffice.

[0053] In Step 4 of the above reaction scheme, a compound of formula (II) is prepared by reacting the compound of formula (VI) prepared as described in Step 3 with *p*-hydroxybenzaldehyde, which has the formula (IIIa), for example as described in Japanese Patent Provisional Publication Tokkai No. Sho 63-139182. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated aliphatic hydrocarbons, such as methylene chloride, 1,2-dichloroethane, chloroform and carbon tetrachloride; ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran and ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene and xylene; water; esters, such as ethyl acetate; amides, especially fatty acid amides, such as dimethylformamide; and mixtures of any two or more of these solvents. The reaction is normally and preferably carried out in the presence of a base, which may be: an inorganic base, such as an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), an alkali metal carbonate (e.g. potassium carbonate or sodium carbonate) or an alkali metal halide (e.g. sodium iodide, sodium bromide or potassium bromide); or an organic base, such as an alkylamine (e.g. triethylamine); or a heterocyclic amine (e.g. morpholine, *N*-ethylpiperidine or pyridine). There is no particular limitation on the ratio of the *p*-hydroxybenzaldehyde to the compound of formula (VI), but the reaction is normally and preferably carried out using from 1 to 3 moles, more preferably from 1.5 to 2.5 moles, of *p*-hydroxybenzaldehyde per mole of the compound of formula (VI). The base is normally and preferably used in an amount of from 1 to 3 moles, more preferably from 1.5 to 2.5 moles, per mole of the compound of formula (VI). The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature in the range of from 50 to 200°C, more preferably from 130 to 180°C. The time required for the reaction may likewise vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, in most cases, a period of from a few hours to 10 or more hours will normally suffice.

[0054] Step 5 of this reaction scheme provides an alternative to Steps 2 to 4. In Step 5, a compound of formula (II) is prepared directly from the compound of formula (IV) and *p*-hydroxybenzaldehyde of formula (IIIa) by a coupling reaction, for example as described in Japanese Patent Provisional Publication Tokkai No. Hei 1-131169. Examples of coupling agents which may be employed in this reaction include diethyl azodicarboxylate and triphenylphosphine. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated aliphatic hydrocarbons, such as methylene chloride, 1,2-dichloroethane, chloroform or carbon tetrachloride; ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran or ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene or xylene; esters, such as ethyl acetate; amides, especially fatty acid amides, such as dimethylformamide; and mixtures of any two or more of these solvents. There is no particular limitation on the ratio of the compound of formula (IV) to the coupling agent, e.g. diethyl azodicarboxylate and triphenylphosphine, but it is preferred to use a slight molar excess of the coupling agent. We prefer to use from 1 to 2 moles, more preferably from 1.0 to 1.5 moles, of the coupling agent per mole of the compound of formula (IV). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0 to 70°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from a few minutes to 10 or more hours will usually suffice.

[0055] Step 6 of this reaction scheme provides a further alternative to Steps 2 to 4. In Step 6, a compound of formula (II) is prepared by reacting the compound of formula (IV), prepared as described in Step 1, with a *p*-halobenzaldehyde of formula (IIIb) (particularly *p*-fluorobenzaldehyde), which reaction may, for example, be carried out as described in Japanese Patent Provisional Publication Tokkai No. Hei 1-131169. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated aliphatic hydrocarbons, such as methylene chloride, 1,2-dichloroethane, chloroform or carbon tetrachloride; ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran or ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene or xylene; amides, such as dimethylformamide; sulphoxides, such as dimethyl sulphoxide; and sulphones, such as sulfolane. In general,

the reaction is preferably carried out in the presence of a base, which is preferably an essentially inorganic base, such as an alkali metal carbonate (e.g. potassium carbonate or sodium carbonate), an alkali metal hydride (e.g. sodium hydride); an alkali metal acetate (e.g. potassium acetate or sodium acetate); or an alkali metal alkoxide (e.g. sodium methoxide or sodium ethoxide). There is no particular limitation on the ratio of the p-halobenzaldehyde to the compound of formula (IV), but it is preferred to use a slight molar excess of the p-halobenzaldehyde to the compound of formula (IV). In general, we prefer to use from 1 to 2 moles, more preferably from 1.0 to 1.5 moles, of the p-halo- benzaldehyde per mole of the compound of formula (IV). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 100 to 170°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvents employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from a few minutes to 10 or more hours will usually suffice.

[0056] Step 7 of this reaction scheme provides an alternative to Steps 3 and 4. In Step 7, a compound of formula (V), prepared as described in Step 2, is reacted with p-hydroxybenzaldehyde of formula (IIIa), for example by the procedure described in Japanese Patent Provisional Publication Tokkai No. Sho 63-139182 to give a compound of formula (II). The reaction is essentially the same as that described in Step 4, and may be carried out in a similar manner to the procedure described in Step 4.

[0057] Steps 8 and 9 provide a further alternative to Steps 3 and 4.

[0058] In Step 8, a compound of formula (V), prepared as described in Step 2, is reacted with a p-halophenol of formula (IVb) to give a compound of formula (VII). The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated aliphatic hydrocarbons, such as methylene chloride, 1,2-dichloroethane, chloroform and carbon tetrachloride; ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran and ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene and xylene; water; esters, such as ethyl acetate; amides, especially fatty acid amides, such as dimethylformamide; and mixtures of any two or more of these solvents. The reaction is normally and preferably carried out in the presence of a base, which may be: an inorganic base, such as an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide) or an alkali metal carbonate (e.g. potassium carbonate or sodium carbonate); or an organic base, such as an alkylamine (e.g. triethylamine) or a heterocyclic amine (e.g. morpholine, N-ethylpiperidine or pyridine). There is no particular limitation on the ratio of the p-halophenol of formula (IVb) to the compound of formula (V), but it is preferred to use a slight excess of the p-halophenol over the compound of formula (V). More preferably the reaction is carried out using from 1 to 2 moles, most preferably from 1.0 to 1.5 moles, of the p-halophenol per mole of the compound of formula (V). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 10 to 50°C, more preferably from 15 to 30°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvents employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from a few hours to 10 or more hours will usually suffice.

[0059] In Step 9 of this reaction scheme, the compound of formula (II) is prepared by reacting the compound of general formula (VII), prepared as described in Step 8, with butyllithium and dimethylformamide, for example as described in Japanese Patent Provisional Publication Tokkai No. Hei 1-186884. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, dibutyl ether, diisobutyl ether, dioxane, tetrahydrofuran and ethylene glycol dimethyl ether; and aromatic hydrocarbons, such as benzene, toluene and xylene. There is no particular limitation on the relative molar ratios of the compound of formula (VII), butyllithium and dimethylformamide, but, in general, the reaction is preferably carried out using about one mole of butyllithium and about one mole of dimethylformamide per mole of the compound of formula (VII). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -70 to -80°C, more preferably about -80°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from a few hours to 10 or more hours will usually suffice.

[0060] In Step 10, the desired compound of formula (I) is prepared by reacting the compound of formula (II), which may have been prepared by any of the routes outlined above, with 2,4-thiazolidinedione, for example according to the procedure described in Japanese Patent Provisional Publication Tokkai No. Sho 63-139182. The reaction is preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents,

at least to some extent. Examples of suitable solvents include: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; amides, especially fatty acid amides, such as dimethylformamide; sulfoxides, such as dimethyl sulfoxide; sulphones, such as sulfolane; ethers, such as dioxane, ethylene glycol dimethyl ether and tetrahydrofuran; ketones, such as acetone; nitriles, such as acetonitrile; organic acids, such as acetic acid; water; and mixtures of any two or more of these solvents. The reaction is normally and preferably carried out in the presence of a base, which may be: an inorganic base, such as an alkali metal carbonate (e.g. potassium carbonate or sodium carbonate), an alkali metal hydride (e.g. sodium hydride), an alkali metal acetate (e.g. potassium acetate or sodium acetate), an alkali metal alkoxide (e.g. sodium methoxide or sodium ethoxide) or ammonia; or an organic base, such as an alkylamine (e.g. methylamine, ethylamine, diethylamine or triethylamine); or a heterocyclic amine (e.g. morpholine, pyrrolidine, piperidine, N-ethylpiperidine, piperazine or pyridine). There is no particular limitation on the ratio of the compound of formula (II) to the 2,4-thiazolidinedione, but the reaction is preferably carried out using from 1 to 4 moles, more preferably from 1 to 2.5 moles, of the 2,4-thiazolidinedione per mole of the compound of formula (II) and from 0.05 to 1 mole, more preferably from 0.2 to 0.6 mole, of the base per mole of the compound of formula (II). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 40°C to the reflux temperature of the reaction mixture, more preferably from 80 to 150°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several tens of minutes to several tens of hours will usually suffice.

[0061] Alternatively, the compound of formula (I) may also be prepared by reacting 5-(4-hydroxybenzylidene)-2,4-thiazolidinedione [which may have been prepared, for example, as described in J. Med. Chem., 14, 528 (1971) or "Nippon Kagaku Zasshi" (the Journal of the Chemical Society of Japan), 92, 867 (1971)] with the compound of formula (VI), prepared as described in Step 3, or with the compound of formula (V), prepared as described in Step 2. In carrying out this alternative process, the reaction may be carried out in a similar manner and using similar reaction conditions to those described in Step 4 or Step 7, respectively.

[0062] In the compounds of formulae (I) through (VII), where R³ and/or R⁴ represents a hydroxy group, R³ and/or R⁴ can, if desired, be transformed to an alkylcarbonyloxy group, an arylcarbonyloxy group (which may optionally have one or more substituents on the aromatic ring) or an alkoxy group (which may optionally have one or more substituents), all as defined above for R³ and/or R⁴, by using the reactions described in the following optional steps. These reactions can be carried out, for example, as described in Japanese Patent Provisional Publication Tokkai No. Sho 62-5980.

[0063] Thus, compounds of formulae (I) through (VII) where R³ and/or R⁴ represents an alkylcarbonyloxy group or an arylcarbonyloxy group (whose aryl moiety may optionally have one or more substituents) can be prepared by contacting the corresponding compounds wherein R³ and/or R⁴ represents a hydroxy group with an acylating agent, which may be an alkylcarboxylic or arylcarboxylic acid, or an acid halide or acid anhydride thereof, corresponding to the carbonyloxy group which it is desired to introduce. The reaction is preferably effected in the presence of a dehydrating agent or catalyst, such as an inorganic acid (e.g. hydrochloric acid or sulphuric acid) or an organic acid (e.g. p-toluenesulphonic acid). The reaction is normally carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and xylene; aliphatic hydrocarbons, such as hexane, cyclohexane and heptane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride and chloroform; ketones, such as acetone and methyl ethyl ketone; amides, especially fatty acid amides, such as dimethylformamide; sulfoxides, such as dimethyl sulfoxide; sulphones, such as sulfolane; organic bases, such as pyridine and triethylamine; water; and mixtures of any two or more of these solvents. There is no particular limitation on the ratio of the starting compound and the acylating agent, but the reaction is preferably carried out using a slight molar excess of the acylating agent, more preferably from 1 to 10 moles of the acylating agent per mole of the starting compound. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0 to 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several minutes to 10 or more hours will usually suffice.

[0064] Those compounds of formulae (I) through (VII) where R³ and/or R⁴ represents an alkoxy group (which may optionally have one or more substituents) may be prepared by contacting the corresponding compounds wherein R³ and/or R⁴ represents a hydroxy group with an alkyl halide (preferably bromide) which may have one or more substituents, preferably in the presence of a base. The reaction is normally carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable

solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene and xylene; aliphatic hydrocarbons, such as hexane, cyclohexane and heptane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride and chloroform; ketones, such as acetone and methyl ethyl ketone; amides, especially fatty acid amides, such as dimethylformamide; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulfolane; water; and mixtures of any two or more of these solvents. Examples of the bases which may be used in this reaction include: inorganic bases, such as an alkali metal carbonate (e.g. sodium carbonate or potassium carbonate), an alkali metal bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate), an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), an alkaline earth metal hydroxide (e.g. calcium hydroxide), an alkali metal hydride (e.g. sodium hydride or potassium hydride), an alkali metal alkoxides (e.g. sodium methoxide, sodium ethoxide or potassium t-butoxide), an organic lithium compound (e.g. butyllithium or t-butyllithium), a lithium dialkylamide (e.g. lithium diisopropylamide or lithium dicyclohexylamide) or ammonia; and organic bases, such as an alkylamine (e.g. methylamine, ethylamine, diethylamine or triethylamine) or a heterocyclic amine (e.g. morpholine, pyrrolidine, piperidine, N-ethylpiperidine, piperazine or pyridine). The ratio of the alkyl halides to the starting compound is preferably from 1 to 10 moles of alkyl halide per mole of the starting compound, and the ratio of the base to the starting compound is preferably from 1 to 10 moles of the base per mole of the starting compound. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10 to 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several minutes to several days will usually suffice.

[0065] Furthermore, those compounds where R³ and/or R⁴ represents an alkoxy group which is substituted by a substituted or unsubstituted carbamoyl group of formula -CONR⁶R⁷, can be prepared by amidation of the corresponding compound having a carboxy or alkoxycarbonyl group with ammonia or with an amine, by conventional means. Alternatively, a compound wherein R³ and/or R⁴ represents an alkoxy group substituted with a carbamoyl group can be prepared from the corresponding compound wherein R³ and/or R⁴ represents a hydroxy group by reaction of the compound wherein R³ and/or R⁴ represents a hydroxy group with a carbamoylalkyl halide in the presence of two equivalents of sodium hydride in dimethylformamide.

[0066] Conversely, those compounds of formulae (I) through (VII) where R³ and/or R⁴ represents an alkylcarbonyloxy group, an arylcarbonyloxy group (which may optionally have one or more substituents on the aromatic ring) or an alkoxy group (which may optionally have one or more substituents) can, if desired, be converted to the corresponding compounds where R³ and/or R⁴ represents a hydroxy group. The reaction can be carried out, for example, as described in Japanese Patent Provisional Publication Tokkai No. Sho 62-5980. This reaction is a conventional hydrolysis reaction and may be carried out using any reagent commonly used in the art for this type of reaction, for example: an inorganic acid such as hydrochloric acid, sulphuric acid or nitric acid; or an organic acid such as p-toluenesulphonic acid. The reaction is normally carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: alcohols, such as methanol, ethanol, propanol or butanol; ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; ketones, such as acetone or methyl ethyl ketone; amides, especially fatty acid amides, such as dimethylformamide; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulfolane; organic acids, such as acetic acid or propionic acid; water; and mixtures of any two or more of these solvents. Preferred solvents include water and organic acids, such as acetic acid. The amount of acid used is preferably from 0.001 to 5 moles, more preferably from 0.01 to 1 mole, per mole of the starting compound. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from room temperature to 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several minutes to 10 or more hours will usually suffice.

[0067] Similarly, where W represents a group of formula >C=N-OV (wherein V represents a hydrogen atom, an alkylcarbonyl group, an arylcarbonyl group or an alkyl group which may optionally have one or more substituents), any group or atom represented by V can be converted to any other group or atom so represented by a similar reaction to those described above in relation to the groups represented by R³ and R⁴.

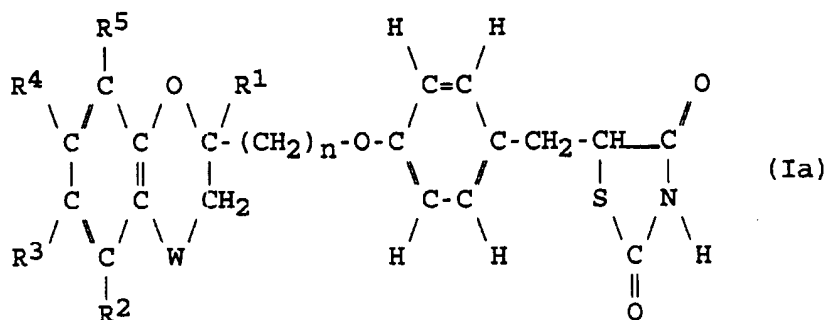
[0068] Thus, when V represents a hydrogen atom, it can be converted to an alkylcarbonyl group, an arylcarbonyl group or an alkyl group which may optionally be substituted, and conversely when V represents an alkylcarbonyl group, an arylcarbonyl group or an alkyl group which may optionally be substituted, it can be converted to a hydrogen atom by hydrolysis according to the procedure described above.

[0069] Furthermore, in the compounds of formulae (I) through (VII), where R³ and/or R⁴ represents a formyl group, an alkylcarbonyl group, an arylcarbonyl group (which may optionally have one or more substituents on the aromatic ring), a carboxy group, an alkoxy carbonyl group, an aryloxy carbonyl group or a halogen atom, these compounds can be converted into each other, if necessary, by any appropriate combination of oxidation, reduction, halogenation, hydrolysis or neutralization according to conventional means.

[0070] After completion of any or all of the above reactions, the desired compounds obtained in any reaction can be separated from the reaction mixture and then purified, if necessary, by conventional means, for example the various chromatography techniques, notably column chromatography, recrystallization or reprecipitation. For example, in one suitable recovery procedure, the reaction mixture is mixed with a solvent and extracted with that solvent; the mixture is then freed from the solvent by distillation. The resulting residue may be purified by column chromatography through silica gel to yield the desired compound as a pure specimen.

[0071] If required, the resolution of isomers can be carried out by conventional resolution and purification techniques at any appropriate time.

[0072] The benzylidenethiazolidine compounds of formula (I) according to the present invention are useful as intermediates for preparing the corresponding benzylthiazolidine compounds (for example, see Japanese Patent Provisional Publication Tokkai No. Sho 60-51189, No. Sho 62-5980, No. Sho 64-38090 and the like), i.e. compounds of formula (Ia):



(in which R¹ to R⁵, W and n are as defined above) by reduction.

[0073] The preparation of the benzylthiazolidine derivatives from the benzylidenethiazolidine compounds of the present invention may be carried out by means of a conventional reduction of a carbon-carbon double bond to a carbon-carbon single bond. The reaction may be carried out using any reducing agent known to be capable of reducing a carbon-carbon double bond to a carbon-carbon single bond without adversely affecting other parts of the molecule.

[0074] For example, one suitable reduction reaction comprises contacting the benzylidenethiazolidine compound of formula (I) with hydrogen in the presence of a noble metal catalyst, which is preferably supported, such as platinum, palladium or rhodium, particularly palladium-on-charcoal. The reaction is normally and preferably carried out in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; alcohols, such as methanol, ethanol, isopropanol or butanol; aromatic hydrocarbons, such as benzene or toluene; amides, especially fatty acid amides, such as dimethylformamide or dimethylacetamide; carboxylic acids, such as formic acid, acetic acid or propionic acid; water; and mixtures of any two or more thereof. Hydrogenation may be carried out under atmospheric pressure or, more preferably, under superatmospheric pressure in a closed pressure vessel. The amount of catalyst used is preferably from 0.01 to 25% by weight of the compound of formula (I). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0 to 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several minutes to 10 or more hours will usually suffice.

[0075] An alternative reduction reaction comprises contacting the benzylidenethiazolidine compound with a metal amalgam, such as sodium amalgam or aluminium amalgam, particularly sodium amalgam. The reaction is effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to

some extent. Examples of suitable solvents include: alcohols, such as methanol. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several minutes to 10 or more hours will usually suffice.

[0076] A further alternative reduction method comprises treating the benzylidenethiazolidine compound with a metal, e.g. zinc, iron or tin in an acid, which may be an inorganic acid (e.g. hydrochloric acid, hydrobromic acid or sulphuric acid) or an organic acid (e.g. acetic acid). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several minutes to 10 or more hours will usually suffice.

[0077] After completion of the reaction, the desired benzylthiazolidine derivatives can be separated from the reaction mixture and can then be purified by conventional means, such as column chromatography, recrystallization, reprecipitation and the like.

[0078] The compounds of the present invention exhibited the ability to inhibit the formation of lipid peroxide in the mammalian body in the test system described by Malvy *et al.* [Biochem. Biophys. Res. Commun., 95, 734 (1980)]. Accordingly, these compounds may be used for the treatment of human arteriosclerosis and complications thereof.

[0079] The compounds of the invention may be administered orally, for example in the form of tablets, syrups, capsules, powders or granules, or parenterally, for example by injection (intravenous, subcutaneous or intramuscular) or in the form of a suppository. Alternatively, they may be formulated for topical administration, e.g. to the eyes. For example, for administration to the eye mucosa, it is preferred that the compounds of the invention should be administered in the form of eye drops or eye ointments, the formulation of which is well known in the art. Depending upon the nature of the formulation, they may be used alone or in admixture with one or more conventional adjuvants. Examples include excipients, binders, disintegrating agents, lubricants, corrigents, solubilizing agents, suspension aids and coating agents.

[0080] The recommended dosage will, of course, vary depending upon the age and body weight of the patient as well as the nature and severity of the disease, and the intended route of administration. However, for an adult human patient, a daily dose of from 5.0 mg to 2000 mg (which may be administered in a single dose or in divided doses) is recommended in the treatment of hyperlipaemia, diabetes mellitus and complications thereof, when administered orally or parenterally.

[0081] The invention is further illustrated by the following Examples, which show the preparation of certain of the compounds of the present invention, and by the subsequent Preparations, of which Preparations 1, 2 and 3 show the preparation of some of the starting materials used in these Examples and Preparations 4, 5 and 6 show the use of the compounds of the present invention in the preparation of their corresponding benzyl derivatives. In these Examples and Preparations, the Nuclear Magnetic Resonance Spectra were measured in the solvent specified in each case, scanning at either 60 MHz or 270 MHz, as specified, and using tetramethylsilane as the internal standard. Certain of the compounds of the invention are identified by Compound Nos., and, in those cases, reference is made to foregoing Tables 1 and 2.

EXAMPLE 1

5-[4-(6-Benzoyloxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione (Compound No. 1-41).

[0082] 4.7 g of 2,4-thiazolidinedione and 0.92 g of piperidine were added to a solution of 11.6 g of 6-benzoyloxy-2-[4-(4-formylphenyl)oxymethyl]-2,5,7,8-tetramethylchroman (prepared as described in Preparation 3) dissolved in 60 ml of 2-methoxyethanol, and the resulting mixture was heated under reflux for 1.5 hours. At the end of this time, the reaction mixture was extracted with methylene chloride. The extract was washed with water, and then the solvent was removed by distillation under reduced pressure. The residue thus obtained was recrystallized from methanol, to afford 11.2 g of the title compound, melting at 190 - 193°C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 60 MHz), δ ppm:

- 1.33 (3H, singlet);
- 1.83 - 2.33 (2H, multiplet);
- 1.97 (3H, singlet);
- 2.10 (6H, singlet);

2.40 - 2.90 (2H, multiplet);
 4.07 (2H, singlet);
 4.63 (2H, singlet);
 7.10 (2H, doublet, J = 9 Hz);
 7.40 (5H, singlet);
 7.47 (2H, doublet, J = 9 Hz);
 7.73 (1H, singlet).

EXAMPLE 2

5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione (Compound No. 1-37)

[0083] 4.74 g of 2,4-thiazolidinedione and 0.92 g of piperidine were added to a solution of 10.3 g of 6-acetoxy-2-(4-formylphenyl)oxymethyl]-2,5,7,8-tetramethylchroman (prepared by a procedure similar to that described in Preparations 1, 2 and 3) dissolved in 60 ml of 2-methoxyethanol, and the resulting mixture was heated under reflux for 1.5 hours. At the end of this time, the reaction mixture was treated in a similar manner to that described in Example 1, to afford 10.0 g of the title compound, melting at 203 - 205.5°C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 60 MHz), δ ppm:

1.40 (3H, singlet);
 1.80 - 2.17 (2H, multiplet);
 1.97 (6H, singlet);
 2.03 (3H, singlet);
 2.30 (3H, singlet);
 2.43 - 2.90 (2H, multiplet);
 4.03 (2H, singlet);
 7.00 (2H, doublet, J = 9 Hz);
 7.40 (2H, doublet, J = 9 Hz);
 7.67 (1H, singlet).

EXAMPLE 3

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione (Compound No. 1-27)

[0084] 15 ml of concentrated hydrochloric acid were added to a solution of 15.4 g of 5-[4-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (prepared as described in Example 1) dissolved in 60 ml of acetic acid, and the resulting mixture was heated under reflux for 1.5 hours. At the end of this time, the reaction mixture was mixed with 200 ml of ethyl acetate and 100 ml of water, and the pH was adjusted to a value of 7 by the addition of a 2N aqueous solution of sodium hydroxide. The ethyl acetate layer was separated and was washed with water to remove impurities, and the aqueous layer was extracted with ethyl acetate to separate the desired compound. After the same washing and extraction procedures had been repeated twice, the combined ethyl acetate extracts were concentrated by distillation under reduced pressure. The residue thus obtained was washed with methanol and 11.6 g of the title compound were collected by filtration.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 60 MHz), δ ppm:

1.43 (3H, singlet);
 2.10 (6H, singlet);
 2.13 (3H, singlet);
 2.20 - 2.43 (2H, multiplet);
 2.47 - 2.90 (2H, multiplet);
 3.70 - 5.53 (1H, broad);
 4.03 (2H, singlet);
 7.03 (2H, doublet, J = 9 Hz);
 7.50 (2H, doublet, J = 9 Hz);
 7.87 (1H, singlet).

EXAMPLE 45-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione (Compound No. 1-37)

- 5 [0085] 0.71 g of acetic anhydride and 0.55 g of pyridine were added to a solution of 1.5 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (prepared as described in Example 3) dissolved in 7.5 ml of toluene, and the resulting mixture was stirred at room temperature for 5 hours. At the end of this time, the reaction mixture was washed with water, and the solvent was removed by distillation under reduced pressure. After trituration with methanol, the crystals thus obtained were collected by filtration to afford 1.2 g of the title compound.
- 10 [0086] The nuclear magnetic resonance spectrum of this compound was identical to that of the product of Example 2.

EXAMPLE 5

15 5-[4-(6-t-Butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (Compound No. 1-98)

- [0087] 500 mg of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (prepared as described in Example 3) were dissolved in 10 ml of dimethylformamide, and 220 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were added to the resulting solution, whilst ice-cooling. The resulting mixture was then stirred at room temperature for 40 minutes. At the end of this time, the mixture was again ice-cooled, and 240 mg of t-butyl bromoacetate were added dropwise to it; it was then stirred for 45 minutes, whilst ice-cooling. At the end of this time, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate and freed from the solvent by distillation under reduced pressure. The residue thus obtained was subjected to column chromatography through silica gel, using a 3 : 1 by volume mixture of hexane and ethyl acetate as the eluent, to afford 360 mg of the title compound as a pale yellow powder, softening at 103 - 120°C.
- 25 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz), δ ppm:

- 1.42 (3H, singlet);
 1.53 (9H, singlet);
 30 1.85 - 2.0 (1H, multiplet);
 2.05 (3H, singlet);
 2.05 - 2.2 (1H, multiplet);
 2.15 (3H, singlet);
 2.19 (3H, singlet);
 35 2.62 (2H, broad triplet, J = 6 Hz);
 3.97 and 4.04 (2H, AB type, J = 9 Hz);
 4.17 (2H, singlet);
 7.02 (2H, doublet, J = 9 Hz);
 7.44 (2H, doublet, J = 9 Hz);
 40 7.80 (1H, singlet);
 8.06 (1H, broad singlet).

EXAMPLE 6

45 5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (Compound No. 1-45)

- [0088] A mixture of 350 mg of 5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (prepared as described in Example 5) and 3 ml of a 4N solution of hydrogen chloride in dioxane was allowed to stand overnight at room temperature. At the end of this time, the reaction mixture was freed from the solvent by distillation under reduced pressure. The residue thus obtained was subjected to column chromatography through silica gel using a 3 : 1 : 0.5 by volume mixture of hexane, ethyl acetate and acetic acid as the eluent, to afford 180 mg of the title compound as a pale yellow powder, melting at 197 - 199°C.
- 55 Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz), δ ppm:

- 1.32 (3H, singlet);
 1.8 - 2.1 (2H, multiplet);
 1.94 (3H, singlet);

2.08 (6H, singlet);
 2.60 (2H, broad triplet, J = 6 Hz);
 4.07 and 4.11 (2H, AB type, J = 10 Hz);
 4.18 (2H, singlet);
 5 7.14 (2H, doublet, J = 9 Hz);
 7.54 (2H, doublet, J = 9 Hz);
 7.75 (1H, singlet);
 12.50 (1H, broad singlet).

10 EXAMPLE 7

5-[4-[6-(1-Ethoxycarbonyl-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione (Compound No. 1-53)

15 **[0089]** Following the procedure described in Example 5, but using 300 mg of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (prepared as described in Example 3) 150 mg of ethyl α -bromoisobutyrate, 70 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) and 5 ml of dimethylformamide, 170 mg of the title compound, melting at 69 - 72°C, were obtained.
 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz), δ ppm:

20 1.35 (3H, triplet, J = 7 Hz);
 1.41 (9H, singlet);
 1.85 - 2.2 (2H, multiplet);
 2.02 (3H, singlet);
 25 2.06 (3H, singlet);
 2.10 (3H, singlet);
 2.60 (2H, broad triplet, J = 6 Hz);
 3.98 and 4.04 (2H, AB type, J = 9 Hz);
 4.27 (2H, quartet, J = 7 Hz);
 30 7.01 (2H, doublet, J = 9 Hz);
 7.44 (2H, doublet, J = 9 Hz);
 7.80 (1H singlet);
 8.07 (1H, broad singlet).

35 EXAMPLE 8

5-[4-[6-(1-Carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione (Compound No. 1-52)

40 **[0090]** A mixture of 60 mg of 5-[4-[6-(1-ethoxycarbonyl-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione (prepared as described in Example 7), 0.25 ml of a 2N aqueous solution of sodium hydroxide and 1 ml of methanol was allowed to stand at room temperature for 3 days. At the end of this time, the reaction mixture was acidified with dilute aqueous hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate, and then the solvent was removed by distillation under reduced pressure, to
 45 afford 40 mg of the title compound as a pale yellow powder.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz), δ ppm:

1.29 (6H, singlet);
 1.32 (3H, singlet);
 50 1.8 - 2.1 (2H, multiplet);
 1.92 (3H, singlet);
 2.04 (6H, singlet);
 2.59 (2H, broad triplet, J = 6 Hz);
 4.10 (2H, broad singlet);
 55 7.13 (2H, doublet, J = 9 Hz);
 7.53 (2H, doublet, J = 9 Hz);
 7.75 (1H, singlet);
 12.50 (1H, broad singlet).

PREPARATION 16-Benzoyloxy-2,5,7,8-tetramethylchroman-2-methyl methanesulphonate

- 5 [0091] 25.54 g of methanesulphonyl chloride were added dropwise, whilst ice-cooling, to a solution of 56.57 g of 6-benzoyloxy-2,5,7,8-tetramethylchroman-2-methanol dissolved in 560 ml of methylene chloride, and the resulting mixture was heated under reflux for 1 hour. At the end of this time, the reaction mixture was washed with water, and the solvent was removed by distillation under reduced pressure. After the residue had been triturated with methanol, the crystals thus obtained were collected by filtration to afford 68.43 g of the title compound, melting at 90 - 96°C.
- 10 Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz), δ ppm:

- 1.30 (3H, singlet);
 1.70 - 2.03 (2H, multiplet);
 2.10 (3H, singlet);
 15 2.13 (3H, singlet);
 2.20 (3H, singlet);
 2.43 - 2.87 (2H, multiplet);
 2.97 (3H, singlet);
 4.17 (2H, singlet);
 20 4.67 (2H, singlet);
 7.10 - 7.63 (5H, multiplet).

PREPARATION 26-Benzoyloxy-2-iodomethyl-2,5,7,8-tetramethylchroman

- [0092] 224.8 g of sodium iodide were added to a solution of 40.44 g of 6-benzoyloxy-2,5,7,8-tetramethylchroman-2-methyl methanesulphonate (prepared as described in Preparation 1) dissolved in 600 ml of dimethylformamide, and the resulting mixture was heated under reflux for 4 hours. At the end of this time, the reaction mixture was extracted with 200 ml of hexane. The extract was washed with water, and the solvent was removed by distillation under reduced pressure. After the residue had been triturated with methanol, the crystals thus obtained were collected by filtration to afford 29.14 g of the title compound, melting at 95 - 98°C.
- 30 Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz), δ ppm:

- 35 1.47 (3H, singlet);
 1.80 - 2.10 (2H, multiplet);
 2.13 (6H, singlet);
 2.20 (3H, singlet);
 2.33 - 2.80 (2H, multiplet);
 40 3.30 (2H, singlet);
 4.67 (2H, singlet);
 7.17 - 7.63 (5H, multiplet).

PREPARATION 3

45 6-Benzoyloxy-2-[(4-formylphenyl)oxymethyl]-2,5,7,8-tetramethylchroman

- [0093] A mixture of 1.63 g of sodium hydride (as a 55% w/w dispersion in mineral oil) and 20 ml of dimethylformamide was cooled in an atmosphere of nitrogen; to the cooled solution were then added dropwise a mixture of 4.58 g of p-hydroxybenzaldehyde and 30 ml of dimethylformamide, whilst ice-cooling. 10.9 g of 6-benzoyloxy-2-iodomethyl-2,5,7,8-tetramethylchroman (prepared as described in Preparation 2) and 50 ml of dimethylformamide were then added to the resulting solution, and the resulting mixture was heated under reflux for 5.5 hours. At the end of this time, the reaction mixture was extracted twice, each time with 100 ml of ethyl acetate. The combined extracts were washed with water, and the solvent was then removed from the extract by distillation under reduced pressure to afford 10.5 g of the title compound as an oil.
- 50
- 55 Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz), δ ppm:

- 1.43 (3H, singlet);

1.63 - 2.27 (2H, multiplet);
 2.03 (3H, singlet);
 2.13 (3H, singlet);
 2.20 (3H, singlet);
 5 2.43 - 2.90 (2H, multiplet);
 4.00 (2H, singlet);
 4.63 (2H, singlet);
 6.97 (2H, doublet, J = 9 Hz);
 7.10 - 7.60 (5H, multiplet);
 10 7.77 (2H, doublet, J = 9 Hz);
 9.77 (1H, singlet).

PREPARATION 4

15 5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzyl]-2,4-thiazolidinedione

[0094] 1.5 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione (prepared as described in Example 3) was dissolved in a mixture of 200 ml of acetic acid and 3 ml of water and catalytically reduced at 60 - 70°C for 3 hours under a pressure of 4 kg/cm² of hydrogen in the presence of 1.5 g of 10% w/w palladium-on-charcoal. At the end of this time, 1.3 g of the title compound, melting at 184 - 186°C, was obtained from the reaction mixture.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone, 60 MHz), δ ppm:

1.39 (3H, singlet);
 25 about 2 (2H, multiplet);
 2.02 (3H, singlet);
 2.09 (3H, singlet);
 2.13 (3H, singlet);
 2.63 (2H, broad triplet, J = 6 Hz);
 30 3.07 (1H, doublet of doublets, J = 15 & 9 Hz);
 3.41 (1H, doublet of doublets, J = 15 & 4.5 Hz);
 3.97 (2H, J = 9 Hz);
 4.70 (1H, doublet of doublets, J = 15 & 4.5 Hz);
 6.90 (2H, doublet, J = 9 Hz);
 35 7.21 (2H, doublet, J = 9Hz).

PREPARATION 5

40 5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzyl]-2,4-thiazolidinedione

[0095] 4.3 g of 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione were dissolved in a mixture of 200 ml of acetic acid and 20 ml of water and catalytically reduced at 55 - 70°C under a pressure of 3 kg/cm² of hydrogen for 2.5 hours in the presence of 4.3 g of 10% w/w palladium-on-charcoal. At the end of this time, the catalyst was removed by filtration from the reaction mixture. The solvent was removed from the filtrate by distillation under reduced pressure, and the residue thus obtained was mixed with 80 ml of ethyl acetate and 80 ml of water. The pH of the mixture was adjusted to a value of 7 by the addition of a 2N aqueous solution of sodium hydroxide. The ethyl acetate layer was extracted with 80 ml of water to remove impurities. The aqueous layer was then extracted with 80 ml of ethyl acetate to give the desired compound. The operation was repeated twice. The combined extracts were freed from the solvent by distillation under reduced pressure to afford 3.4 g of the title compound.

50 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz), δ ppm:

3.03 (1H, doublet of doublets, J = 15, 9 Hz);
 3.42 (1H, doublet of doublets, J = 15, 4.5 Hz);
 4.45 (1H, doublet of doublets, J = 9, 4.5Hz).

55

PREPARATION 6

5-[4-[6-(1-Carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzyl]-2,4-thiazolidinedione

[0096] Following a procedure similar to that described in Preparation 5, the title compound is synthesized by reduction of 5-[4-[6-(1-carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione, prepared as described in Example 8.

[0097] The benzylthiazolidine compound prepared in Preparation 6 above is a known compound and is described in Japanese Patent Provisional Publication (Tokkai) No. Sho. 62-5980 (Example 79). This benzylthiazolidine compound is an excellent inhibitor of aldose reductase activity. Accordingly, the benzylidenethiazolidine compound employed as a starting material in this Preparation is useful as a synthetic intermediate for preparing the corresponding benzylthiazolidine compound.

BIOLOGICAL ACTIVITY

Inhibitory activity on the formation of lipid peroxide

[0098] This was investigated by the ferrous sulphate/cysteine method described by Malvy *et al.* [Biochem. Biophys. Res. Commun., 95, 734 (1980)]. The compound under test at various concentrations, cysteine (500 μ M) and ferrous sulphate (5 μ M) were added to and allowed to react with a rat liver microsomal preparation. The amount of lipid peroxide thus formed was measured according to the thiobarbituric acid (TBA) method and the concentration of the compound under test required to inhibit the formation of lipid peroxide by 50% (I_{50} μ g/ml) was calculated. The results are reported in Table 3, below. The compounds of the invention are identified by the number of the Example in which their preparation is illustrated.

Table 3

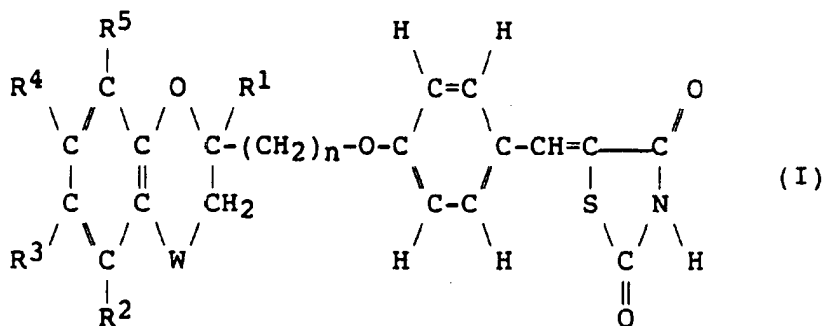
Example No.	Concentration inhibiting 50% of the lipid peroxide formation (μ g/ml)
2	0.03 - 0.1
3	0.03 - 0.1

[0099] The results shown above demonstrate that the compounds of the present invention strongly inhibit the formation of lipid peroxide, even at low concentrations.

Claims

Claims for the following Contracting States : GB, DE, FR, IT, CH, DK, BE, NL, SE, LI, LU, AT

1. A compound of formula (I):



in which R¹, R² and R⁵ are the same or different and each represents a hydrogen atom or an alkyl group

having from 1 to 10 carbon atoms;

R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; a carboxy group; an alkoxycarbonyl group having from 2 to 7 carbon atoms; an aryloxy group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; a formyloxy group; an arylcarbonyloxy group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; an alkoxy group having from 1 to 5 carbon atoms; a substituted alkoxy group having from 1 to 5 carbon atoms and substituted by at least one of substituents (b), defined below; or a halogen atom;

W represents a methylene group, a carbonyl group or a group of formula $>C=N-OV$

wherein V represents: a hydrogen atom; an alkylcarbonyl group having from 2 to 6 carbon atoms; an arylcarbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; an alkyl group having from 1 to 5 carbon atoms; or a substituted alkyl group having from 1 to 5 carbon atoms and substituted by at least one of substituents (d), defined below; and

n is an integer of from 1 to 3;

substituents (a) :

alkyl groups having from 1 to 5 carbon atoms; alkoxy groups having from 1 to 5 carbon atoms; and halogen atoms;

substituents (b) :

aryl groups which have from 6 to 10 ring carbon atoms and which are unsubstituted or which are substituted by at least one of substituents (a), defined above; carboxy groups; alkoxycarbonyl groups having from 2 to 6 carbon atoms; and groups of formula $-CONR^6R^7$, where

R^6 and R^7 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 5 carbon atoms; or an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or which is substituted by at least one of substituents (a), defined above; or R^6 and R^7 , together with the nitrogen atom to which they are attached, form a heterocyclic group which has from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (c), defined below;

substituents (c) :

alkyl groups having from 1 to 5 carbon atoms; and aryl groups which have from 6 to 10 ring carbon atoms and which are unsubstituted or which are substituted by at least one of substituents (a), defined above;

substituents (d) :

carboxy groups and alkoxycarbonyl groups having from 2 to 6 carbon atoms;

and pharmaceutically acceptable salts thereof.

2. Compounds according to Claim 1, in which R^1 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms
3. Compounds according to Claim 1 or Claim 2, in which R^2 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms.
4. Compounds according to any one of Claims 1 to 3, in which R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5

carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a carboxy group; an alkoxy-carbonyl group having from 2 to 7 carbon atoms; an aryloxy-carbonyl group having from 7 to 11 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms, whose aryl moiety is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a halogen atom; or an alkoxy group having from 1 to 5 carbon atoms which is unsubstituted or is substituted by from one to three substituents, the substituents being selected from

(1) aryl groups having from 6 to 10 carbon atoms which themselves are unsubstituted or are substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms,

(2) carboxy groups,

(3) alkoxy-carbonyl groups having from 2 to 6 carbon atoms,

(4) groups of formula $-\text{CONR}^6\text{R}^7$, in which R^6 and R^7 are the same or different and each represents

[1] a hydrogen atom,

[2] an alkyl group having from 1 to 5 carbon atoms,

[3] an aryl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or

[4] R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted or being substituted by at least one substituent, the substituent being selected from alkyl groups having from 1 to 5 carbon atoms and aryl groups having from 6 to 10 carbon atoms, which themselves are unsubstituted or are substituted by from 1 to 5 substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms.

5. Compounds according to any one of Claims 1 to 4, in which R^5 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms.

6. Compounds according to any one of Claims 1 to 5, in which W represents a methylene group, a carbonyl group, or a group of formula $>\text{C}=\text{N}-\text{OV}$, in which V represents:
a hydrogen atom, an alkylcarbonyl group having from 2 to 6 carbon atoms, an arylcarbonyl group having from 7 to 11 carbon atoms, or an alkyl group having from 1 to 5 carbon atoms, said alkyl group being unsubstituted or being substituted by from one to three substituents, the substituents being selected from

carboxy groups and

alkoxy-carbonyl groups having from 2 to 6 carbon atoms.

7. Compounds according to any one of Claims 1 to 6, in which \underline{n} is 1 or 2.

8. Compounds according to Claim 1, in which:

R^1 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

R^2 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a carboxy group; an alkoxy-carbonyl group having from 2 to 7 carbon atoms; an aryloxy-carbonyl group having from 7 to 11 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms, whose aryl moiety is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a halogen atom; or an alkoxy group having from 1 to 5 carbon atoms which is unsubstituted or is

substituted by from one to three substituents, the substituents being selected from

- (1) aryl groups having from 6 to 10 carbon atoms which themselves are unsubstituted or are substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms,
- (2) carboxy groups,
- (3) alkoxycarbonyl groups having from 2 to 6 carbon atoms,
- (4) groups of formula $-\text{CONR}^6\text{R}^7$, in which R^6 and R^7 are the same or different and each represents

- [1] a hydrogen atom,
- [2] an alkyl group having from 1 to 5 carbon atoms,
- [3] an aryl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or
- [4] R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted or being substituted by at least one substituent, the substituent being selected from alkyl groups having from 1 to 5 carbon atoms and aryl groups having from 6 to 10 carbon atoms, which themselves are unsubstituted or are substituted by from 1 to 5 substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms;

R^5 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

W represents a methylene group, a carbonyl group, or a group of formula $>\text{C}=\text{N}-\text{OV}$, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 6 carbon atoms, an arylcarbonyl group having from 7 to 11 carbon atoms, or an alkyl group having from 1 to 5 carbon atoms, said alkyl group being unsubstituted or being substituted by from one to three substituents, the substituents being selected from

carboxy groups and
alkoxycarbonyl groups having from 2 to 6 carbon atoms; and

n is 1 or 2.

9. Compounds according to Claim 1, in which R^1 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.
10. Compounds according to Claim 1 or Claim 9, in which R^2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.
11. Compounds according to any one of Claims 1, 9 and 10, in which R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 4 carbon atoms; an alkylcarbonyl group having from 2 to 7 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a carboxy group; an alkoxycarbonyl group having from 2 to 5 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 7 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a halogen atom; or an alkoxy group having from 1 to 3 carbon atoms, said group being unsubstituted or being substituted by one or two substituents, the substituents being selected from
 - [1] aryl groups having from 6 to 10 carbon atoms and whose aryl moiety is unsubstituted,
 - [2] carboxy groups,
 - [3] alkoxycarbonyl groups having from 2 to 5 carbon atoms,
 - [4] carbamoyl groups, and
 - [5] groups of formula $-\text{CONR}^6\text{R}^7$, in which R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted.
12. Compounds according to any one of Claims 1 and 9 to 11, in which R^5 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

13. Compounds according to any one of Claims 1 and 9 to 12, in which W represents a methylene group or a group of formula $>C=N-OV$, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 4 carbon atoms, or a benzoyl group.
14. Compounds according to Claim 1, in which:
- R^1 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;
- R^2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;
- R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 4 carbon atoms; an alkylcarbonyl group having from 2 to 7 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a carboxy group; an alkoxycarbonyl group having from 2 to 5 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 7 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a halogen atom; or an alkoxy group having from 1 to 3 carbon atoms, said group being unsubstituted or being substituted by one or two substituents, the substituents being selected from
- [1] aryl groups having from 6 to 10 carbon atoms and whose aryl moiety is unsubstituted,
- [2] carboxy groups,
- [3] alkoxycarbonyl groups having from 2 to 5 carbon atoms,
- [4] carbamoyl groups, and
- [5] groups of formula $-CONR^6R^7$, in which R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted;
- R^5 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;
- W represents a methylene group or a group of formula $>C=N-OV$, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 4 carbon atoms, or a benzoyl group; and
- n is 1 or 2.
15. Compounds according to Claim 1, in which R^1 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.
16. Compounds according to Claim 1 or Claim 15, in which R^2 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.
17. Compounds according to any one of Claims 1, 15 and 16, in which R^3 represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxy, methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-methylethoxy, carbamoylmethoxy, piperidinocarbonylmethoxy or morpholinocarbonylmethoxy group, or a chlorine or fluorine atom.
18. Compounds according to any one of Claims 1 and 15 to 17, in which R^4 represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted, a carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)-propoxy or 1-(t-butoxycarbonyl)-1-methylethoxy group, or a chlorine or fluorine atom.
19. Compounds according to any one of Claims 1 and 15 to 18, in which R^5 represents a hydrogen atom, or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

20. Compounds according to any one of Claims 1 and 15 to 19, in which W represents a methylene group or a group of formula $>C=N-OV$, in which V represents a hydrogen atom or an acetyl group.
21. Compounds according to Claim 1, in which:
- 5 R1 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group;
- R2 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group;
- 10 R3 represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, a benzoyloxy, methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)-propoxy, 1-(t-butoxycarbonyl)-1-methylethoxy, carbamoylmethoxy, piperidinocarbonylmethoxy or morpholinocarbonylmethoxy group, or a chlorine or fluorine atom;
- 15 R4 represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted, a carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy or 1-(t-butoxycarbonyl)-1-methylethoxy group, or a chlorine or fluorine atom;
- 20 R5 represents a hydrogen atom, or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group;
- 25 W represents a methylene group or a group of formula $>C=N-OV$, in which V represents a hydrogen atom or an acetyl group; and
- 30 \underline{n} is 1 or 2.
22. Compounds according to Claim 1, in which R¹ represents a methyl group.
23. Compounds according to Claim 1 or Claim 22, in which R² represents a hydrogen atom or a methyl group.
24. Compounds according to any one of Claims 1, 22 and 23, in which R³ represents a hydrogen atom, a methyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, hydroxy, acetoxymethoxy, methoxy, benzyloxy, carboxymethoxy or 3-carboxypropoxy group, or a fluorine atom.
25. Compounds according to any one of Claims 1 and 22 to 24, in which R⁴ represents a hydrogen atom, a methyl, t-butyl, acetyl, hydroxy, acetoxymethoxy, benzoyloxy, carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group or a fluorine atom.
26. Compounds according to any one of Claims 1 and 22 to 25, in which R⁵ represents a hydrogen atom or a methyl group.
27. Compounds according to any one of Claims 1 and 22 to 26, in which W represents a methylene group.
28. Compounds according to any one of Claims 1 and 22 to 27, in which \underline{n} is 1.
29. Compounds according to Claim 1, in which:
- 55 R1 represents a methyl group;
- R2 represents a hydrogen atom or a methyl group;
- R3 represents a hydrogen atom, a methyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbo-

nyl, hydroxy, acetoxy, methoxy, benzyloxy, carboxymethoxy or 3-carboxypropoxy group, or a fluorine atom;

R⁴ represents a hydrogen atom, a methyl, t-butyl, acetyl, hydroxy, acetoxy, benzoyloxy, carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group or a fluorine atom;

R⁵ represents a hydrogen atom or a methyl group;

W represents a methylene group; and

n is 1.

30. 5-[4-(2-Methylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

31. 5-[4-(2,5,7-Trimethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

32. 5-[4-(2,5,6,7,8-Pentamethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

33. 5-[4-(7-Hydroxy-2,8-dimethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

34. 5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

35. 5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

36. 5-[4-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

37. 5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

38. 5-[4-[6-(3-Carboxypropoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

39. 5-[4-[6-(1-Carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

40. 5-[4-(6-Carbamoylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

41. 5-[4-[6-(Piperidinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

42. 5-[4-[6-(Morpholinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

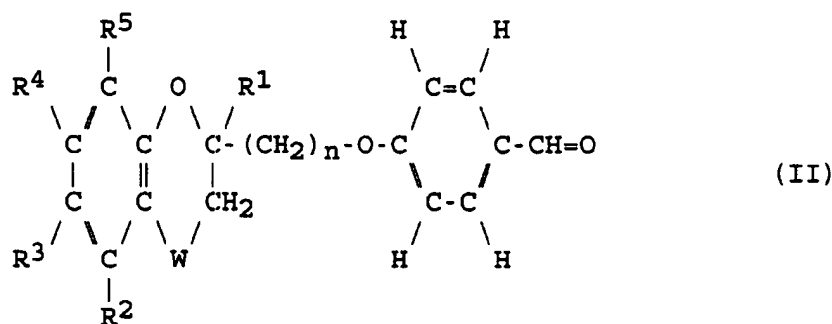
43. 5-[4-(6-Carboxy-2-methylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione and pharmaceutically acceptable salts thereof.

44. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding Claims, in admixture with a pharmaceutically acceptable carrier or diluent.

45. Compounds of formula (I) and pharmaceutically acceptable salts thereof, as claimed in any one of Claims 1 to 44, for use in therapy.

46. The use of compounds of formula (I) and pharmaceutically acceptable salts thereof, as claimed in any one of Claims 1 to 44, for the manufacture of a medicament for reducing lipid peroxide levels in an animal.

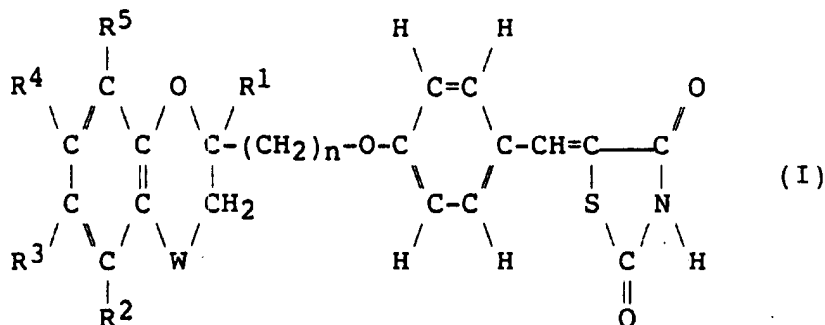
47. A process for preparing a compound according to any one of Claims 1 to 44, which comprises:
reacting a compound of formula (II):



(in which R¹, R², R³, R⁴, R⁵, n and W are as defined in Claim 1) with thiazolidine-2,4-dione.

Claims for the following Contracting States : ES, GR

1. A process for preparing a compound of formula (I):



[in which R¹, R² and R⁵ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

R³ and R⁴ are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; a carboxy group; an alkoxycarbonyl group having from 2 to 7 carbon atoms; an aryloxy carbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; a formyloxy group; an arylcarbonyloxy group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; an alkoxy group having from 1 to 5 carbon atoms; a substituted alkoxy group having from 1 to 5 carbon atoms and substituted by at least one of substituents (b), defined below; or a halogen atom;

W represents a methylene group, a carbonyl group or a group of formula $>C=N-OV$

wherein V represents: a hydrogen atom; an alkylcarbonyl group having from 2 to 6 carbon atoms; an arylcarbonyl group in which the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one of substituents (a), defined below; an alkyl group having from 1 to 5 carbon atoms; or a substituted alkyl group having from 1 to 5 carbon atoms and substituted by at least one of substituents (d), defined below; and

n is an integer of from 1 to 3;

substituents (a) :

alkyl groups having from 1 to 5 carbon atoms; alkoxy groups having from 1 to 5 carbon atoms; and halogen atoms;

substituents (b) :

aryl groups which have from 6 to 10 ring carbon atoms and which are unsubstituted or which are substituted by at least one of substituents (a), defined above; carboxy groups; alkoxycarbonyl groups having from 2 to 6 carbon atoms; and groups of formula $-CONR^6R^7$, where

R^6 and R^7 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 5 carbon atoms; or an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or which is substituted by at least one of substituents (a), defined above; or R^6 and R^7 , together with the nitrogen atom to which they are attached, form a heterocyclic group which has from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (c), defined below;

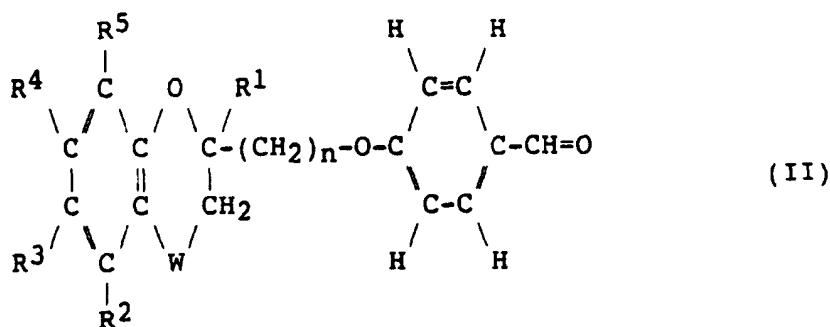
substituents (c) :

alkyl groups having from 1 to 5 carbon atoms; and aryl groups which have from 6 to 10 ring carbon atoms and which are unsubstituted or which are substituted by at least one of substituents (a), defined above;

substituents (d) :

carboxy groups and alkoxycarbonyl groups having from 2 to 6 carbon atoms];

and salts thereof, which process comprises reacting a compound of formula (II):



(in which R^1 , R^2 , R^3 , R^4 , R^5 , n and W are as defined above) with thiazolidine-2,4-dione.

2. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R^1 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms.
3. A process according to Claim 1 or Claim 2, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R^2 represents a hydrogen atom or an alkyl

group having from 1 to 10 carbon atoms.

4. A process according to any one of Claims 1 to 3, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a carboxy group; an alkoxycarbonyl group having from 2 to 7 carbon atoms; an aryloxycarbonyl group having from 7 to 11 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms, whose aryl moiety is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a halogen atom; or an alkoxy group having from 1 to 5 carbon atoms which is unsubstituted or is substituted by from one to three substituents, the substituents being selected from

(1) aryl groups having from 6 to 10 carbon atoms which themselves are unsubstituted or are substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms,

(2) carboxy groups,

(3) alkoxycarbonyl groups having from 2 to 6 carbon atoms,

(4) groups of formula $-\text{CONR}^6\text{R}^7$, in which R^6 and R^7 are the same or different and each represents

[1] a hydrogen atom,

[2] an alkyl group having from 1 to 5 carbon atoms,

[3] an aryl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or

[4] R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted or being substituted by at least one substituent, the substituent being selected from alkyl groups having from 1 to 5 carbon atoms and aryl groups having from 6 to 10 carbon atoms, which themselves are unsubstituted or are substituted by from 1 to 5 substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms.

5. A process according to any one of Claims 1 to 4, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R^5 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms.

6. A process according to any one of Claims 1 to 5, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which W represents a methylene group, a carbonyl group, or a group of formula

$>\text{C}=\text{N}-\text{OV}$, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 6 carbon atoms, an arylcarbonyl group having from 7 to 11 carbon atoms, or an alkyl group having from 1 to 5 carbon atoms, said alkyl group being unsubstituted or being substituted by from one to three substituents, the substituents being selected from

carboxy groups and

alkoxycarbonyl groups having from 2 to 6 carbon atoms.

7. A process according to any one of Claims 1 to 6, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which n is 1 or 2.

8. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which:

R^1 represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

R² represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

R³ and R⁴ are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 10 carbon atoms; a formyl group; an alkylcarbonyl group having from 2 to 11 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a carboxy group; an alkoxycarbonyl group having from 2 to 7 carbon atoms; an aryloxy carbonyl group having from 7 to 11 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 11 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms, whose aryl moiety is unsubstituted or is substituted by from one to five substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms; a halogen atom; or an alkoxy group having from 1 to 5 carbon atoms which is unsubstituted or is substituted by from one to three substituents, the substituents being selected from

- (1) aryl groups having from 6 to 10 carbon atoms which themselves are unsubstituted or are substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms,
- (2) carboxy groups,
- (3) alkoxycarbonyl groups having from 2 to 6 carbon atoms,
- (4) groups of formula -CONR⁶R⁷, in which R⁶ and R⁷ are the same or different and each represents

- [1] a hydrogen atom,
- [2] an alkyl group having from 1 to 5 carbon atoms,
- [3] an aryl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by from one to five substituents on the aromatic ring, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or
- [4] R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted or being substituted by at least one substituent, the substituent being selected from alkyl groups having from 1 to 5 carbon atoms and aryl groups having from 6 to 10 carbon atoms, which themselves are unsubstituted or are substituted by from 1 to 5 substituents, the substituents being selected from alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms;

R⁵ represents a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms;

W represents a methylene group, a carbonyl group, or a group of formula >C=N-OV, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 6 carbon atoms, an arylcarbonyl group having from 7 to 11 carbon atoms, or an alkyl group having from 1 to 5 carbon atoms, said alkyl group being unsubstituted or being substituted by from one to three substituents, the substituents being selected from

carboxy groups and
alkoxycarbonyl groups having from 2 to 6 carbon atoms; and

n is 1 or 2.

9. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R¹ represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.
10. A process according to Claim 1 or Claim 9, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R² represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.
11. A process according to any one of Claims 1, 9 and 10, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R³ and R⁴ are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 4 carbon atoms; an alkylcarbonyl group having from 2 to 7 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms and whose aryl moiety is

unsubstituted; a carboxy group; an alkoxycarbonyl group having from 2 to 5 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 7 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a halogen atom; or an alkoxy group having from 1 to 3 carbon atoms, said group being unsubstituted or being substituted by one or two substituents, the substituents being selected from

- [1] aryl groups having from 6 to 10 carbon atoms and whose aryl moiety is unsubstituted,
- [2] carboxy groups,
- [3] alkoxycarbonyl groups having from 2 to 5 carbon atoms,
- [4] carbamoyl groups, and
- [5] groups of formula $-\text{CONR}^6\text{R}^7$, in which R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted.

12. A process according to any one of Claims 1 and 9 to 11, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R^5 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

13. A process according to any one of Claims 1 and 9 to 12, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which W represents a methylene group or a group of formula $>\text{C}=\text{N}-\text{OV}$, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 4 carbon atoms, or a benzoyl group.

14. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which:

R^1 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;

R^2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;

R^3 and R^4 are the same or different and each represents: a hydrogen atom; an alkyl group having from 1 to 4 carbon atoms; an alkylcarbonyl group having from 2 to 7 carbon atoms; an arylcarbonyl group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a carboxy group; an alkoxycarbonyl group having from 2 to 5 carbon atoms; a hydroxy group; an alkylcarbonyloxy group having from 2 to 7 carbon atoms; an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted; a halogen atom; or an alkoxy group having from 1 to 3 carbon atoms, said group being unsubstituted or being substituted by one or two substituents, the substituents being selected from

- [1] aryl groups having from 6 to 10 carbon atoms and whose aryl moiety is unsubstituted,
- [2] carboxy groups,
- [3] alkoxycarbonyl groups having from 2 to 5 carbon atoms,
- [4] carbamoyl groups, and
- [5] groups of formula $-\text{CONR}^6\text{R}^7$, in which R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated heterocyclic group having from 3 to 7 ring atoms, of which 1 is said nitrogen atom and 0 or 1 is an additional oxygen or nitrogen atom, the group being unsubstituted;

R^5 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;

W represents a methylene group or a group of formula $>\text{C}=\text{N}-\text{OV}$, in which V represents: a hydrogen atom, an alkylcarbonyl group having from 2 to 4 carbon atoms, or a benzoyl group; and

n is 1 or 2.

15. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R^1 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

16. A process according to Claim 1 or Claim 15, in which the reagents and reaction conditions are so selected as to

prepare a compound of formula (I) or a salt or ester thereof in which R² represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

17. A process according to any one of Claims 1, 15 and 16, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R³ represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, a benzoyloxy, methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-methylethoxy, carbamoylmethoxy, piperidinocarbonylmethoxy or morpholinocarbonylmethoxy group, or a chlorine or fluorine atom.

18. A process according to any one of Claims 1 and 15 to 17, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R⁴ represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted, a carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy or 1-(t-butoxycarbonyl)-1-methylethoxy group, or a chlorine or fluorine atom.

19. A process according to any one of Claims 1 and 15 to 18, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R⁵ represents a hydrogen atom, or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

20. A process according to any one of Claims 1 and 15 to 19, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which W represents a methylene group or a group of formula >C=N-OV, in which V represents a hydrogen atom or an acetyl group.

21. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which:

R¹ represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group;

R² represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group;

R³ represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, a benzoyloxy, methoxy, benzyloxy, carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)-propoxy, 1-(t-butoxycarbonyl)-1-methylethoxy, carbamoylmethoxy, piperidinocarbonylmethoxy or morpholinocarbonylmethoxy group, or a chlorine or fluorine atom;

R⁴ represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl group, an alkylcarbonyl group having from 2 to 5 carbon atoms, a benzoyl group, a hydroxy group, an alkylcarbonyloxy group having from 2 to 5 carbon atoms, an arylcarbonyloxy group having from 7 to 11 carbon atoms and whose aryl moiety is unsubstituted, a carboxymethoxy, 3-carboxypropoxy, 1-carboxy-1-methylethoxy, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, 1-methoxycarbonyl-1-methylethoxy, t-butoxycarbonylmethoxy, 3-(t-butoxycarbonyl)propoxy or 1-(t-butoxycarbonyl)-1-methylethoxy group, or a chlorine or fluorine atom;

R⁵ represents a hydrogen atom, or a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group;

W represents a methylene group or a group of formula >C=N-OV, in which V represents a hydrogen atom or an acetyl group; and

n is 1 or 2.

22. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R¹ represents a methyl group.
23. A process according to Claim 1 or Claim 22, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R² represents a hydrogen atom or a methyl group.
24. A process according to any one of Claims 1, 22 and 23, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R³ represents a hydrogen atom, a methyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, hydroxy, acetoxymethoxy, benzyloxy, carboxymethoxy or 3-carboxypropoxy group, or a fluorine atom.
25. A process according to any one of Claims 1 and 22 to 24, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R⁴ represents a hydrogen atom, a methyl, t-butyl, acetyl, hydroxy, acetoxymethoxy, benzoyloxy, carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group or a fluorine atom.
26. A process according to any one of Claims 1 and 22 to 25, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which R⁵ represents a hydrogen atom or a methyl group.
27. A process according to any one of Claims 1 and 22 to 26, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which W represents a methylene group.
28. A process according to any one of Claims 1 and 22 to 27, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which n is 1.
29. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare a compound of formula (I) or a salt or ester thereof in which:
- R¹ represents a methyl group;
- R² represents a hydrogen atom or a methyl group;
- R³ represents a hydrogen atom, a methyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, hydroxy, acetoxymethoxy, benzyloxy, carboxymethoxy or 3-carboxypropoxy group, or a fluorine atom;
- R⁴ represents a hydrogen atom, a methyl, t-butyl, acetyl, hydroxy, acetoxymethoxy, benzoyloxy, carboxymethoxy, 3-carboxypropoxy or 1-carboxy-1-methylethoxy group or a fluorine atom;
- R⁵ represents a hydrogen atom or a methyl group;
- W represents a methylene group; and
- n is 1.
30. A process according to Claim 1 in which the reagents and reaction conditions are so selected as to prepare:
- 5-[4-(2-methylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 5-[4-(2,5,7-trimethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 5-[4-(2,5,6,7,8-pentamethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;
- 5-[4-(7-hydroxy-2,8-dimethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;

5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;

5-[4-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzylidene]-2,4-thiazolidinedione;

5-[4-(6-carboxymethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-(3-carboxypropoxy)-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-(1-carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-carbamoylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-(piperidinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-(morpholinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

5-[4-(6-carboxy-2-methylchroman-2-methoxy)benzylidene]-2,4-thiazolidinedione;

or a salt thereof.

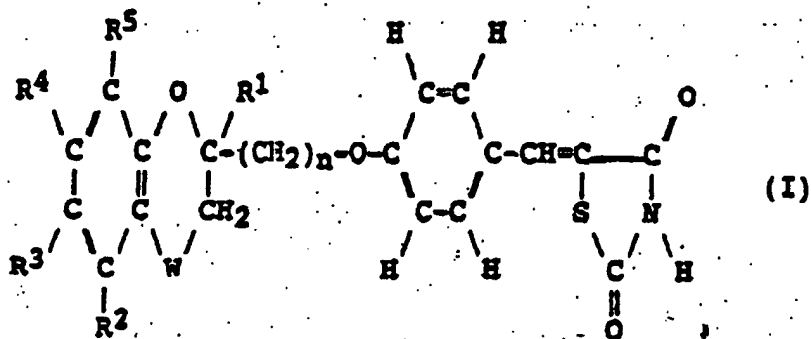
31. A process for preparing a pharmaceutical composition comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier or diluent.

32. The use of compounds of formula (I) and pharmaceutically acceptable salts thereof, as defined in any one of Claims 1 to 30, for the manufacture of a medicament for reducing lipid peroxide levels in an animal.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : GB, DE, FR, IT, CH, DK, BE, NL, SE, LI, LU, AT

1. Verbindung der Formel (I):



worin R¹, R² und R⁵ gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellen;

R³ und R⁴ gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit

1 bis 10 Kohlenstoffatomen, eine Formylgruppe, eine Alkylcarbonylgruppe mit 2 bis 11 Kohlenstoffatomen, eine Arylcarbonylgruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Carboxygruppe, eine Alkoxy-
 5 carbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Aryloxycarbonylgruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 11 Kohlenstoffatomen, eine Formyloxygruppe, eine Arylcarbonyloxygruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, eine substituierte Alkoxygruppe, die 1 bis 5 Kohlenstoffatome
 10 hat und mit mindestens einem der nachstehend definierten Substituenten (b) substituiert ist, oder ein Halogenatom;

W eine Methylengruppe, eine Carbonylgruppe oder eine Gruppe der Formel $>C=N-OV$ darstellt,

15 worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 6 Kohlenstoffatomen, eine Arylcarbonylgruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder eine substituierte Alkylgruppe, die 1 bis 5 Kohlenstoffatome hat und mit mindestens einem der nachstehend definierten Substituenten (d) substituiert ist, und

20 n eine ganze Zahl von 1 bis 3 ist;

wobei die Substituenten (a) darstellen:

25 Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatome;

wobei die Substituenten (b) darstellen:

Arylgruppen, die 6 bis 10 Ringkohlenstoffatome haben und die unsubstituiert oder mit mindestens einem der vorstehend definierten Substituenten (a) substituiert sind, Carboxygruppen, Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen und Gruppen der Formel $-CONR^6R^7$, worin

30 R^6 und R^7 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder eine Arylgruppe, die 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der vorstehend definierten Substituenten (a) substituiert ist, oder R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe bilden, die 3 bis 7 Ringkohlenstoffatome hat, von denen eines das Stickstoffatom ist und 0 oder 1 ein zusätzliches Stickstoff-
 35 und/oder Sauerstoff- und/oder Schwefelheteroatom ist, wobei die heterocyclische Gruppe unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (c) substituiert ist;

wobei die Substituenten (c) darstellen:

40 Alkylgruppen mit 1 bis 5 Kohlenstoffatomen und Arylgruppen, die 6 bis 10 Ringkohlenstoffatome haben und unsubstituiert oder mit mindestens einem der vorstehend definierten Substituenten (a) substituiert sind;

wobei die Substituenten (d) darstellen:

Carboxygruppen und Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen;

45 und pharmazeutisch geeignete Salze davon.

2. Verbindungen nach Anspruch 1, worin R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt.
- 50 3. Verbindungen nach Anspruch 1 oder 2, worin R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt.
- 55 4. Verbindungen nach einem der Ansprüche 1 bis 3, worin R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen, eine Formylgruppe, eine Alkylcarbonylgruppe mit 2 bis 11 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, die unsubstituiert ist oder mit einem bis fünf Substituenten substituiert ist, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Aryloxycarbonylgruppe mit

7 bis 11 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 11 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, worin der Arylrest unsubstituiert oder mit einem bis fünf Substituenten substituiert ist, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, ein Halogenatom oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, die unsubstituiert oder mit einem bis drei Substituenten substituiert ist, wobei die Substituenten unter den folgenden Gruppen ausgewählt sind:

- (1) Arylgruppen mit 6 bis 10 Kohlenstoffatomen, die selbst unsubstituiert oder mit: 1 bis 5 Substituenten am aromatischen Ring substituiert sind, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind,
- (2) Carboxygruppen,
- (3) Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen und
- (4) Gruppen der Formel $\text{-CONR}^6\text{R}^7$, worin R^6 und R^7 gleich oder unterschiedlich sind und jeweils darstellen:

- [1] ein Wasserstoffatom,
- [2] eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen,
- [3] eine Arylgruppe mit 6 bis 10 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert ist, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, oder
- [4] R^6 und R^7 bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit: 3 bis 7 Ringatomen, worin 1 das Stickstoffatom ist: und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist oder mit mindestens einem Substituenten substituiert ist, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen und Arylgruppen mit 6 bis 10 Kohlenstoffatomen ausgewählt ist, welche selbst unsubstituiert oder mit 1 bis 5 Substituenten substituiert sind, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind.

5. Verbindungen nach einem der Ansprüche 1 bis 4, worin R^5 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt.

6. Verbindungen nach einem der Ansprüche 1 bis 5, worin W eine Methylengruppe, eine Carbonylgruppe oder eine Gruppe der Formel >C=N-OV darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit von 2 bis 6 Kohlenstoffatomen, eine Arylcarbonylgruppe mit von 7 bis 11 Kohlenstoffatomen oder eine Alkylgruppe mit von 1 bis 5 Kohlenstoffatomen, wobei die Alkylgruppe unsubstituiert ist oder mit einem bis drei Substituenten substituiert ist, die unter Carboxygruppen und Alkoxy-carbonylgruppen mit von 2 bis 6 Kohlenstoffatomen ausgewählt sind.

7. Verbindungen nach einem der Ansprüche 1 bis 6, worin n 1 oder 2 ist.

8. Verbindungen nach Anspruch 1, worin:

- R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt;
- R^2 ein Wasserstoffatom oder eine Alkylgruppe mit von 1 bis 10 Kohlenstoffatomen darstellt;
- R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit von 1 bis 10 Kohlenstoffatomen, eine Formylgruppe, eine Alkylcarbonylgruppe mit von 2 bis 11 Kohlenstoffatomen, eine Arylcarbonylgruppe mit von 7 bis 11 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 5 Substituenten substituiert ist, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit von 2 bis 7 Kohlenstoffatomen, eine Aryloxycarbonylgruppe mit von 7 bis 11 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit von 2 bis 11 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit von 7 bis 11 Kohlenstoffatomen, deren Arylrest unsubstituiert ist oder mit 1 bis 5 Substituenten substituiert ist, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, ein Halogenatom oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, die unsubstituiert ist oder mit einem bis drei Substituenten substituiert ist, die aus der folgenden Gruppe ausgewählt sind:

- (1) Arylgruppen mit 6 bis 10 Kohlenstoffatomen, die selbst unsubstituiert oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert sind, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlen-

stoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind,
 (2) Carboxygruppen,
 (3) Alkoxy-carbonylgruppen mit von 2 to 6 Kohlenstoffatomen und
 (4) Gruppen der Formel $-\text{CONR}^6\text{R}^7$, worin R^6 und R^7 gleich oder unterschiedlich sind und jeweils darstellen:

[1] ein Wasserstoffatom,
 [2] eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen,
 [3] eine Arylgruppe mit 6 bis 10 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert ist, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, oder
 [4] R^6 und R^7 bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen, worin 1 das Stickstoffatom ist: und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist oder mit mindestens einem Substituenten substituiert ist, der unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen und Arylgruppen mit 6 bis 10 Kohlenstoffatomen ausgewählt ist, welche selbst unsubstituiert oder mit 1 to 5 Substituenten substituiert sind, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 to 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind;

R^5 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt;
 W eine Methylengruppe, eine Carbonylgruppe oder eine Gruppe der Formel $>\text{C}=\text{N}-\text{OV}$ darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit: 2 bis 6 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen oder eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 3 Substituenten substituiert ist, die unter Carboxygruppen und Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen ausgewählt sind; und
 n 1 oder 2 ist.

9. Verbindungen nach Anspruch 1, worin R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt.

10. Verbindungen nach Anspruch 1 oder 9, worin R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt.

11. Verbindungen nach einem der Ansprüche 1, 9 und 10, worin R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen:

ein Wasserstoffatom, eine Alkylgruppe mit von 1 to 4 Kohlenstoffatomen, eine Alkylcarbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 7 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, ein Halogenatom, oder eine Alkoxygruppe mit 1 bis 3 Kohlenstoffatomen, die unsubstituiert ist oder mit einem oder zwei Substituenten substituiert ist, die unter den folgenden Gruppen ausgewählt sind:

[1] Arylgruppen mit 6 bis 10 Kohlenstoffatomen, deren Arylteil unsubstituiert ist,
 [2] Carboxygruppen,
 [3] Alkoxy-carbonylgruppen mit 2 bis 5 Kohlenstoffatomen,
 [4] Carbamoylgruppen und
 [5] Gruppen der Formel $-\text{CONR}^6\text{R}^7$, worin R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen bilden, worin 1 das Stickstoffatom ist und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist.

12. Verbindungen nach einem der Ansprüche 1 und 9 bis 11, worin R^5 ein Wasserstoffatom oder eine Alkylgruppe mit von 1 to 4 Kohlenstoffatomen darstellt.

13. Verbindungen nach einem der Ansprüche 1 und 9 bis 12, worin W eine Methylengruppe oder eine Gruppe der Formel $>\text{C}=\text{N}-\text{OV}$ darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 4 Kohlen-

stoffatomen oder eine Benzoylgruppe.

14. Verbindungen nach Anspruch 1, worin:

- 5 R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt;
- R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt;
- 10 R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkylcarbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 7 Kohlenstoffatomen,
- 15 eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, ein Halogenatom oder eine Alkoxygruppe mit 1 bis 3 Kohlenstoffatomen, die unsubstituiert ist oder mit einem oder zwei Substituenten substituiert ist, die unter den folgenden Gruppen ausgewählt sind:
- [1] Arylgruppen mit 6 bis 10 Kohlenstoffatomen, deren Arylteil unsubstituiert ist,
- [2] Carboxygruppen,
- 20 [3] Alkoxy-carbonylgruppen mit 2 bis 5 Kohlenstoffatomen,
- [4] Carbamoylgruppen und
- [5] Gruppen der Formel $-\text{CONR}^6\text{R}^7$, worin R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen bilden, worin 1 das Stickstoffatom ist und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist;
- 25 R^5 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt;
- W eine Methylengruppe oder eine Gruppe der Formel $>\text{C}=\text{N}-\text{OV}$ darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder eine Benzoylgruppe; und
- 30 n 1 oder 2 ist.

15. Verbindungen nach Anspruch 1, worin R^1 ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt.

16. Verbindungen nach Anspruch 1 oder 15, worin R^2 ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl oder Isobutylgruppe darstellt.

40 17. Verbindungen nach einem der Ansprüche 1, 15 und 16, worin R^3 ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe, eine Alkylcarbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoyloxy-, Methoxy-, Benzoyloxy-, Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy-, 1-(t-Butoxycarbonyl)-1-methylethoxy-, Carbamoylmethoxy-, Piperidinocarbonylmethoxy- oder Morpholinocarbonylmethoxygruppe oder ein Chlor- oder Fluoratom darstellt.

50 18. Verbindungen nach einem der Ansprüche 1 und 15 bis 17, worin R^4 ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sec-Butyl oder t-Butylgruppe, eine Alkylcarbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit von 2 bis 5 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy- oder 1-(t-Butoxycarbonyl)-1-methylethoxygruppe oder ein Chlor- oder Fluoratom darstellt.

55 19. Verbindungen nach einem der Ansprüche 1 und 15 bis 18, worin R^5 ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt.

20. Verbindungen nach einem der Ansprüche 1 und 15 bis 19, worin W eine Methylengruppe oder eine Gruppe der Formel $>C=N-OV$, darstellt, worin V ein Wasserstoffatom oder eine Acetylgruppe darstellt.

21. Verbindungen nach Anspruch 1, worin:

R¹ ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt;

R² ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt;

R³ ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe, eine Alkylcarbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoyloxy-, Methoxy-, Benzyloxy-, Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy-, 1-(t-Butoxycarbonyl)-1-methylethoxy-, Carbamoylmethoxy-, Piperidinocarbonylmethoxy- oder Morpholinocarbonylmethoxygruppe oder ein Chlor- oder Fluoratom bedeutet;

R⁴ ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sec-Butyl- oder t-Butylgruppe, eine Alkylcarbonylgruppe mit von 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 5 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)-propoxy- oder 1-(t-Butoxycarbonyl)-1-methylethoxygruppe oder ein Chlor- oder Fluoratom darstellt;

R⁵ ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt;

W eine Methylengruppe oder eine Gruppe der Formel $>C=N-OV$ darstellt, worin V ein Wasserstoffatom oder eine Acetylgruppe darstellt; und

n 1 oder 2 ist.

22. Verbindungen nach Anspruch 1, worin R¹ eine Methylgruppe darstellt.

23. Verbindungen nach Anspruch 1 oder 22, worin R² ein Wasserstoffatom oder eine Methylgruppe darstellt.

24. Verbindungen nach einem der Ansprüche 1, 22 und 23, worin R³ ein Wasserstoffatom, eine Methyl-, Acetyl-, Carboxy-, Methoxycarbonyl-, Ethoxycarbonyl-, t-Butoxycarbonyl-, Hydroxy-, Acetoxy-, Methoxy-, Benzyloxy-, Carboxymethoxy- oder 3-Carboxypropoxygruppe oder ein Fluoratom darstellt.

25. Verbindungen nach einem der Ansprüche 1 und 22 bis 24, worin R⁴ ein Wasserstoffatom, eine Methyl-, t-Butyl-, Acetyl-, Hydroxy-, Acetoxy-, Benzyloxy-, Carboxymethoxy-, 3-Carboxypropoxy- oder 1-Carboxy-1-methylethoxygruppe oder ein Fluoratom darstellt.

26. Verbindungen nach einem der Ansprüche 1 und 22 bis 25, worin R⁵ ein Wasserstoffatom oder eine Methylgruppe darstellt.

27. Verbindungen nach einem der Ansprüche 1 und 22 bis 26, worin W eine Methylengruppe darstellt.

28. Verbindungen nach einem der Ansprüche 1 und 22 bis 27, worin n 1 ist.

29. Verbindungen nach Anspruch 1, worin:

R¹ eine Methylgruppe darstellt;

R² ein Wasserstoffatom oder eine Methylgruppe darstellt;

R³ ein Wasserstoffatom, eine Methyl-, Acetyl-, Carboxy-, Methoxycarbonyl-, Ethoxycarbonyl-, t-Butoxycarbonyl-, Hydroxy-, Acetoxy-, Methoxy-, Benzyloxy-, Carboxymethoxy- oder 3-Carboxypropoxygruppe oder ein Fluoratom darstellt;

5 R⁴ ein Wasserstoffatom, eine Methyl-, t-Butyl-, Acetyl-, Hydroxy-, Acetoxy-, Benzoyloxy-, Carboxymethoxy-, 3-Carboxypropoxy- oder 1-Carboxy-1-methylethoxygruppe oder ein Fluoratom darstellt;

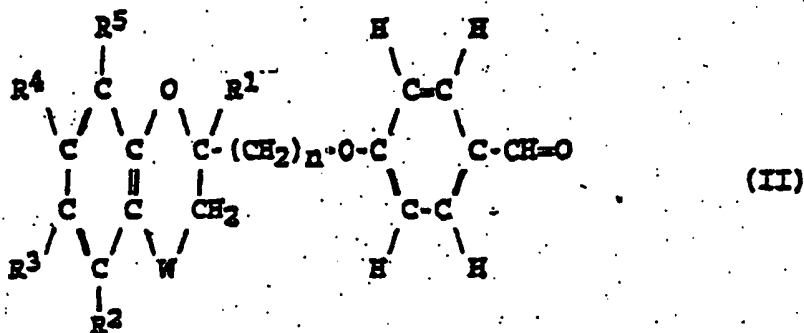
R⁵ ein Wasserstoffatom oder eine Methylgruppe darstellt;

10 W eine Methylengruppe darstellt; und

n 1 ist.

- 15 30. 5-[4-(2-Methylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
31. 5-[4-(2,5,7-Trimethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 20 32. 5-[4-(2,5,6,7,8-Pentamethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
33. 5-[4-(7-Hydroxy-2,8-dimethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 25 34. 5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 30 35. 5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
36. 5-[4-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methoxy)-benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
37. 5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 35 38. 5-[4-[6-(3-Carboxypropoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 40 39. 5-[4-[6-(1-Carboxy-1-methylethoxy)-2,5,7,8-tetra-methylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
40. 5-[4-(6-Carbamoylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 45 41. 5-[4-[6-(Piperidinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
42. 5-[4-[6-(Morpholinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 50 43. 5-[4-(6-Carboxy-2-methylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion und pharmazeutisch geeignete Salze davon.
- 55 44. Arzneimittelzusammensetzung, welches eine Verbindung der Formel (I) oder ein pharmazeutisch geeignetes Salz davon nach einem der vorangehenden Ansprüche zusammen mit einem pharmazeutisch geeigneten Träger oder Verdünnungsmittel enthält.

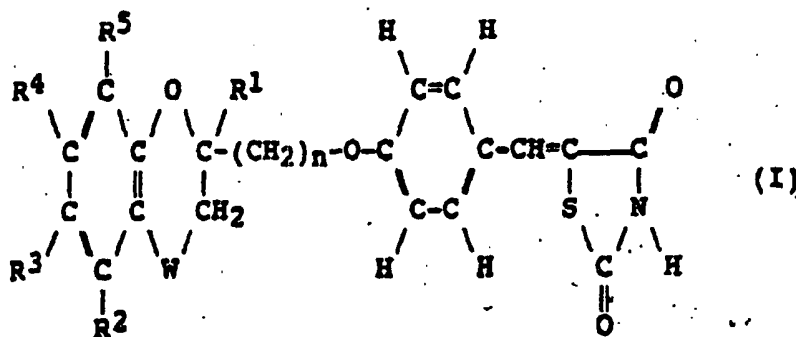
45. Verwendung von Verbindungen der Formel (I) und pharmazeutisch geeigneter Salze davon nach einem der Ansprüche 1 bis 44 in der Therapie.
46. Verwendung von Verbindungen der Formel (I) und pharmazeutisch geeigneter Salze davon nach einem der Ansprüche 1 bis 44 zur Herstellung eines Arzneimittels zur Senkung des Lipidperoxidspiegels in einem Tier.
47. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 44, welches umfasst:
Umsetzen einer Verbindung der Formel (II):



(worin R¹, R², R³, R⁴, R⁵, n und W wie in Anspruch 1 definiert sind) mit Thiazolidin-2,4-dion.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel (I):



worin R¹, R² und R⁵ gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellen;

R³ und R⁴ gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen, eine Formylgruppe, eine Alkylcarbonylgruppe mit 2 bis 11 Kohlenstoffatomen, eine Arylcarbonylgruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Aryloxy-carbonylgruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 11 Kohlenstoffatomen, eine Formyloxygruppe, eine Arylcarbonyloxygruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, eine substituierte Alkoxygruppe, die 1 bis 5 Kohlenstoffatome

hat und mit mindestens einem der nachstehend definierten Substituenten (b) substituiert ist, oder ein Halogenatom;

W eine Methylengruppe, eine Carbonylgruppe oder eine Gruppe der Formel $>C=N-OV$ darstellt,

worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 6 Kohlenstoffatomen, eine Arylcarbonylgruppe, worin der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (a) substituiert ist, eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder eine substituierte Alkylgruppe, die 1 bis 5 Kohlenstoffatome hat und mit mindestens einem der nachstehend definierten Substituenten (d) substituiert ist, und

n eine ganze Zahl von 1 bis 3 ist;

wobei die Substituenten (a) darstellen:

Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatome;

wobei die Substituenten (b) darstellen:

Arylgruppen, die 6 bis 10 Ringkohlenstoffatome haben und die unsubstituiert oder mit mindestens einem der vorstehend definierten Substituenten (a) substituiert sind, Carboxygruppen, Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen und Gruppen der Formel $-CONR^6R^7$, worin

R^6 und R^7 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder eine Arylgruppe, die 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem der vorstehend definierten Substituenten (a) substituiert ist, oder R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe bilden, die 3 bis 7 Ringkohlenstoffatome hat, von denen eines das Stickstoffatom ist und 0 oder 1 ein zusätzliches Stickstoff- und/oder Sauerstoff- und/oder Schwefelheteroatom ist, wobei die heterocyclische Gruppe unsubstituiert oder mit mindestens einem der nachstehend definierten Substituenten (c) substituiert ist;

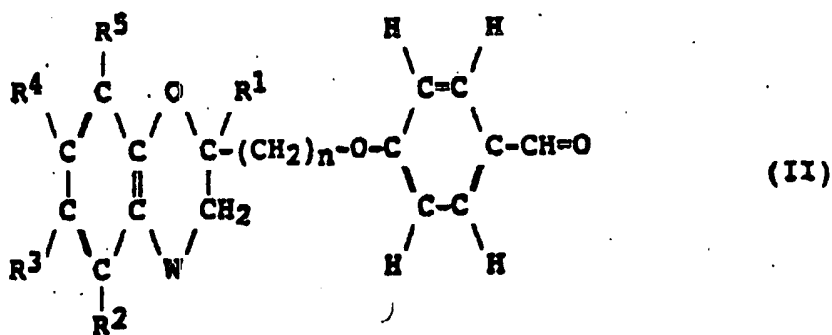
wobei die Substituenten (c) darstellen:

Alkylgruppen mit 1 bis 5 Kohlenstoffatomen und Arylgruppen, die 6 bis 10 Ringkohlenstoffatome haben und unsubstituiert oder mit mindestens einem der vorstehend definierten Substituenten (a) substituiert sind;

wobei die Substituenten (d) darstellen:

Carboxygruppen und Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen;

und Salzen davon, welches das Umsetzen einer Verbindung der Formel (II):



(worin R^1 , R^2 , R^3 , R^4 , R^5 , n und W wie vorstehend definiert sind) mit Thiazolidin-2,4-dion umfaßt.

2. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt.

3. Verfahren nach Anspruch 1 oder 2, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt.
- 5 4. Verfahren nach einem der Ansprüche 1 bis 3, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen, eine Formylgruppe, eine Alkylcarbonylgruppe mit 2 bis 11 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, die unsubstituiert ist oder mit einem bis fünf Substituenten substituiert ist, wobei die
- 10 Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, eine Carboxygruppe, eine Alkoxycarbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Aryloxycarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 11 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, worin der Arylrest unsubstituiert oder mit einem bis fünf Substituenten substituiert ist, wobei die Substituenten unter Alkylgruppen
- 15 mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, ein Halogenatom oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, die unsubstituiert oder mit einem bis drei Substituenten substituiert ist, wobei die Substituenten unter den folgenden Gruppen ausgewählt sind:
- (1) Arylgruppen mit 6 bis 10 Kohlenstoffatomen, die selbst unsubstituiert oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert sind, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind,
- 20 (2) Carboxygruppen,
- (3) Alkoxycarbonylgruppen mit 2 bis 6 Kohlenstoffatomen und
- (4) Gruppen der Formel $-CONR^6R^7$, worin R^6 und R^7 gleich oder unterschiedlich sind und jeweils darstellen:
- 25 [1] ein Wasserstoffatom,
- [2] eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen,
- [3] eine Arylgruppe mit 6 bis 10 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert ist, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, oder
- 30 [4] R^6 und R^7 bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen, worin 1 das Stickstoffatom ist und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist oder mit mindestens einem Substituenten substituiert ist, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen und Arylgruppen mit 6 bis 10 Kohlenstoffatomen ausgewählt ist, welche selbst unsubstituiert oder mit 1 bis 5 Substituenten substituiert sind, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind.
- 35
5. Verfahren nach einem der Ansprüche 1 bis 4, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^5 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt.
- 40
6. Verfahren nach einem der Ansprüche 1 bis 5, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin W eine Methylengruppe, eine Carbonylgruppe oder eine Gruppe der Formel $>C=N-OV$ darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit von 2 bis 6 Kohlenstoffatomen, eine Arylcarbonylgruppe mit von 7 bis 11 Kohlenstoffatomen oder eine Alkylgruppe mit von 1 bis 5 Kohlenstoffatomen, wobei die Alkylgruppe unsubstituiert ist oder mit einem bis drei Substituenten substituiert ist, die unter Carboxygruppen und Alkoxycarbonylgruppen mit von 2 bis 6 Kohlenstoffatomen ausgewählt sind.
- 45
7. Verfahren nach einem der Ansprüche 1 bis 6, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin n 1 oder 2 ist.
- 50
8. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin:
- 55 R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt;
 R^2 ein Wasserstoffatom oder eine Alkylgruppe mit von 1 bis 10 Kohlenstoffatomen darstellt;

R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit von 1 bis 10 Kohlenstoffatomen, eine Formylgruppe, eine Alkylcarbonylgruppe mit von 2 bis 11 Kohlenstoffatomen, eine Arylcarbonylgruppe mit von 7 bis 11 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 5 Substituenten substituiert ist, wobei die Substituenten unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit von 2 bis 7 Kohlenstoffatomen, eine Aryloxy-carbonylgruppe mit von 7 bis 11 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit von 2 bis 11 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit von 7 bis 11 Kohlenstoffatomen, deren Arylrest unsubstituiert ist oder mit 1 bis 5 Substituenten substituiert ist, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, ein Halogenatom oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, die unsubstituiert ist oder mit einem bis drei Substituenten substituiert ist, die aus der folgenden Gruppe ausgewählt sind:

- (1) Arylgruppen mit 6 bis 10 Kohlenstoffatomen, die selbst unsubstituiert oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert sind, wobei die Substituenten unter Alkylgruppen mit: 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind,
- (2) Carboxygruppen,
- (3) Alkoxy-carbonylgruppen mit von 2 to 6 Kohlenstoffatomen und
- (4) Gruppen der Formel $-\text{CONR}^6\text{R}^7$, worin R^6 und R^7 gleich oder unterschiedlich sind und jeweils darstellen:

- [1] ein Wasserstoffatom,
- [2] eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen,
- [3] eine Arylgruppe mit 6 bis 10 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 5 Substituenten am aromatischen Ring substituiert ist, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 bis 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind, oder
- [4] R^6 und R^7 bilden zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen, worin 1 das Stickstoffatom ist: und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist oder mit mindestens einem Substituenten substituiert ist, der unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen und Arylgruppen mit 6 bis 10 Kohlenstoffatomen ausgewählt ist, welche selbst unsubstituiert oder mit 1 to 5 Substituenten substituiert sind, die unter Alkylgruppen mit 1 bis 5 Kohlenstoffatomen, Alkoxygruppen mit 1 to 5 Kohlenstoffatomen und Halogenatomen ausgewählt sind;

R^5 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 10 Kohlenstoffatomen darstellt; W eine Methylengruppe, eine Carbonylgruppe oder eine Gruppe der Formel $>\text{C}=\text{N}-\text{OV}$ darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 6 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen oder eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, die unsubstituiert ist oder mit 1 bis 3 Substituenten substituiert ist, die unter Carboxygruppen und Alkoxy-carbonylgruppen mit 2 bis 6 Kohlenstoffatomen ausgewählt sind; und n 1 oder 2 ist.

9. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt.
10. Verfahren nach Anspruch 1 oder 9, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt.
11. Verfahren nach einem der Ansprüche 1, 9 und 10, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen:

ein Wasserstoffatom, eine Alkylgruppe mit von 1 to 4 Kohlenstoffatomen, eine Alkylcarbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 7 Kohlenstoffatome, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffa-

tomen, deren Arylteil unsubstituiert ist, ein Halogenatom, oder eine Alkoxygruppe mit 1 bis 3 Kohlenstoffatomen, die unsubstituiert ist oder mit einem oder zwei Substituenten substituiert ist, die unter den folgenden Gruppen ausgewählt sind:

- 5 [1] Arylgruppen mit 6 bis 10 Kohlenstoffatomen, deren Arylteil unsubstituiert ist,
 [2] Carboxygruppen,
 [3] Alkoxy-carbonylgruppen mit 2 bis 5 Kohlenstoffatomen,
 [4] Carbamoylgruppen und
 10 [5] Gruppen der Formel $-\text{CONR}^6\text{R}^7$, worin R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen bilden, worin 1 das Stickstoffatom ist und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist.

12. Verfahren nach einem der Ansprüche 1 und 9 bis 11, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^5 ein Wasserstoffatom oder eine Alkylgruppe mit von 1 to 4 Kohlenstoffatomen darstellt.

13. Verfahren nach einem der Ansprüche 1 und 9 bis 12, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin W eine Methylengruppe oder eine Gruppe der Formel $>\text{C}=\text{N}-\text{OV}$ darstellt; worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder eine Benzoylgruppe.

14. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin:

R^1 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt;

R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt;

30 R^3 und R^4 gleich oder unterschiedlich sind und jeweils darstellen: ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkylcarbonylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Arylcarbonylgruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 7 Kohlenstoffatomen,
 35 eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, ein Halogenatom oder eine Alkoxygruppe mit 1 bis 3 Kohlenstoffatomen, die unsubstituiert ist oder mit einem oder zwei Substituenten substituiert ist, die unter den folgenden Gruppen ausgewählt sind:

- 40 [1] Arylgruppen mit 6 bis 10 Kohlenstoffatomen, deren Arylteil unsubstituiert ist,
 [2] Carboxygruppen,
 [3] Alkoxy-carbonylgruppen mit 2 bis 5 Kohlenstoffatomen,
 [4] Carbamoylgruppen und
 45 [5] Gruppen der Formel $-\text{CONR}^6\text{R}^7$, worin R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine gesättigte heterocyclische Gruppe mit 3 bis 7 Ringatomen bilden, worin 1 das Stickstoffatom ist und 0 oder 1 ein zusätzliches Sauerstoff- oder Stickstoffatom ist, wobei die Gruppe unsubstituiert ist;

R^5 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt;

50 W eine Methylengruppe oder eine Gruppe der Formel $>\text{C}=\text{N}-\text{OV}$ darstellt, worin V darstellt: ein Wasserstoffatom, eine Alkylcarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder eine Benzoylgruppe; und

n 1 oder 2 ist.

55 15. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^1 ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt.

16. Verfahren nach Anspruch 1 oder 15, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R² ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt.
17. Verfahren nach einem der Ansprüche 1, 15 und 16, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R³ ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe, eine Alkylcarbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoyloxy-, Methoxy-, Benzyloxy-, Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy-, 1-(t-Butoxycarbonyl)-1-methylethoxy-, Carbamoylmethoxy-, Piperidinocarbonylmethoxy- oder Morpholinocarbonylmethoxygruppe oder ein Chlor- oder Fluoratom darstellt.
18. Verfahren nach einem der Ansprüche 1 und 15 bis 17, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R⁴ ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sec-Butyl- oder t-Butylgruppe, eine Alkylcarbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit von 2 bis 5 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy- oder 1-(t-Butoxycarbonyl)-1-methylethoxygruppe oder ein Chlor- oder Fluoratom darstellt.
19. Verfahren nach einem der Ansprüche 1 und 15 bis 18, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R⁵ ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt.
20. Verfahren nach einem der Ansprüche 1 und 15 bis 19, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin W eine Methylengruppe oder eine Gruppe der Formel >C=N-OV, darstellt, worin V ein Wasserstoffatom oder eine Acetylgruppe darstellt.
21. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin:
- R¹ ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt;
- R² ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt;
- R³ ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe, eine Alkylcarbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Carboxygruppe, eine Alkoxy-carbonylgruppe mit 2 bis 5 Kohlenstoffatomen, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 5 Kohlenstoffatomen, eine Benzoyloxy-, Methoxy-, Benzyloxy-, Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy-, 1-(t-Butoxycarbonyl)-1-methylethoxy-, Carbamoylmethoxy-, Piperidinocarbonylmethoxy- oder Morpholinocarbonylmethoxygruppe oder ein Chlor- oder Fluoratom bedeutet;
- R⁴ ein Wasserstoffatom, eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sec-Butyl- oder t-Butylgruppe, eine Alkylcarbonylgruppe mit von 2 bis 5 Kohlenstoffatomen, eine Benzoylgruppe, eine Hydroxygruppe, eine Alkylcarbonyloxygruppe mit 2 bis 5 Kohlenstoffatomen, eine Arylcarbonyloxygruppe mit 7 bis 11 Kohlenstoffatomen, deren Arylteil unsubstituiert ist, eine Carboxymethoxy-, 3-Carboxypropoxy-, 1-Carboxy-1-methylethoxy-, Methoxycarbonylmethoxy-, 3-Methoxycarbonylpropoxy-, 1-Methoxycarbonyl-1-methylethoxy-, t-Butoxycarbonylmethoxy-, 3-(t-Butoxycarbonyl)propoxy- oder 1-(t-Butoxycarbonyl)-1-methylethoxygruppe oder ein Chlor- oder Fluoratom darstellt;
- R⁵ ein Wasserstoffatom oder eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe darstellt;

W eine Methylengruppe oder eine Gruppe der Formel $>C=N-OV$ darstellt, worin V ein Wasserstoffatom oder eine Acetylgruppe darstellt; und

n 1 oder 2 ist.

5

22. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^1 eine Methylgruppe darstellt.

10

23. Verfahren nach Anspruch 1 oder 22, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^2 ein Wasserstoffatom oder eine Methylgruppe darstellt.

15

24. Verfahren nach einem der Ansprüche 1, 22 und 23, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^3 ein Wasserstoffatom, eine Methyl-, Acetyl-, Carboxy-, Methoxycarbonyl-, Ethoxycarbonyl-, t-Butoxycarbonyl-, Hydroxy-, Acetoxy-, Methoxy-, Benzyloxy-, Carboxymethoxy- oder 3-Carboxypropoxygruppe oder ein Fluoratom darstellt.

20

25. Verfahren nach einem der Ansprüche 1 und 22 bis 24, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^4 ein Wasserstoffatom, eine Methyl-, t-Butyl-, Acetyl-, Hydroxy-, Acetoxy-, Benzoyloxy-, Carboxymethoxy-, 3-Carboxypropoxy- oder 1-Carboxy-1-methylethoxygruppe oder ein Fluoratom darstellt.

25

26. Verfahren nach einem der Ansprüche 1 und 22 bis 25, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin R^5 ein Wasserstoffatom oder eine Methylgruppe darstellt.

30

27. Verfahren nach einem der Ansprüche 1 und 22 bis 26, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin W eine Methylengruppe darstellt.

35

28. Verfahren nach einem der Ansprüche 1 und 22 bis 27, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin n 1 ist.

29. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß eine Verbindung der Formel (I) oder ein Salz oder Ester davon hergestellt wird, worin:

R^1 eine Methylgruppe darstellt;

40

R^2 ein Wasserstoffatom oder eine Methylgruppe darstellt;

R^3 ein Wasserstoffatom, eine Methyl-, Acetyl-, Carboxy-, Methoxycarbonyl-, Ethoxycarbonyl-, t-Butoxycarbonyl-Hydroxy-, Acetoxy-, Methoxy-, Benzyloxy-, Carboxymethoxy- oder 3-Carboxypropoxygruppe oder ein Fluoratom darstellt;

45

R^4 ein Wasserstoffatom, eine Methyl-, t-Butyl-, Acetyl-, Hydroxy-, Acetoxy-, Benzoyloxy-, Carboxymethoxy-, 3-Carboxypropoxy- oder 1-Carboxy-1-methylethoxygruppe oder ein Fluoratom darstellt;

R^5 ein Wasserstoffatom oder eine Methylgruppe darstellt;

50

W eine Methylengruppe darstellt; und

n 1 ist.

55

30. Verfahren nach Anspruch 1, wobei die Reagenzien und Reaktionsbedingungen so ausgewählt sind, daß

5-[4-(2-Methylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,

5-[4-(2,5,7-Trimethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-(2,5,6,7,8-Pentamethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-(7-Hydroxy-2,8-dimethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-(6-Benzoyloxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-[6-(3-Carboxypropoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion,
 5-[4-[6-(1-Carboxy-1-methylethoxy)-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion,
 5-[4-(6-Carbamoylmethoxy-2,5,7,8-tetramethylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion,
 5-[4-[6-(Piperidinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion,
 5-[4-[6-(Morpholinocarbonyl)methoxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyliden]-2,4-thiazolidindion,
 5-[4-(6-Carboxy-2-methylchroman-2-methoxy)benzyliden]-2,4-thiazolidindion

oder ein Salz davon hergestellt wird.

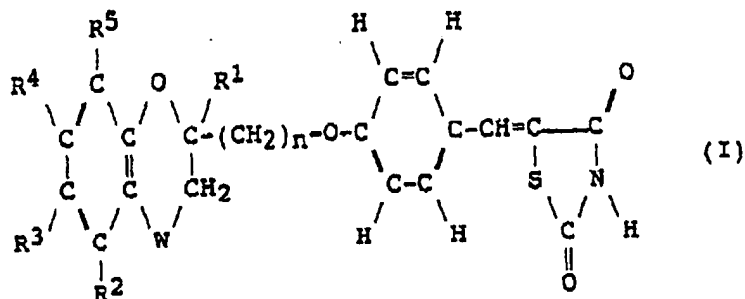
31. Verfahren zur Herstellung einer Arzneimittelszusammensetzung, welches das Mischen einer Verbindung der Formel (I) oder eines pharmazeutisch geeigneten Salzes davon mit einem pharmazeutisch geeigneten Träger oder Verdünnungsmittel umfaßt.

32. Verwendung von Verbindungen der Formel (I) und pharmazeutisch geeigneter Salze davon nach einem der Ansprüche 1 bis 30 für die Herstellung eines Arzneimittels zur Senkung des Lipidperoxidspiegels in einem Tier.

Revendications

Revendications pour les Etats contractants suivants : GB, DE, FR, IT, CH, DK, BE, NL, SE, LI, LU, AT

1. Composé de formule (I) :



dans laquelle R¹, R² et R³ sont identiques ou différents, et chacun représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone;

R³ et R⁴ sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 10 atomes de carbone; un groupe formyle; un groupe alkylcarbonyle comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyle dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe carboxy; un groupe alcoxycarbonyle comportant de 2 à 7 atomes de carbone; un groupe aryloxy carbonyle dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe hydroxy; un groupe alkylcarbonyloxy comportant de 2 à 11 atomes de carbone; un groupe formyloxy; un groupe arylcarbonyloxy dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe alcoxy comportant de 1 à 5 atomes de carbone; un groupe alcoxy substitué comportant de 1 à 5 atomes de carbone et substitué par au moins un des substituants (b) définis ci-dessous; ou un atome d'halogène;

W représente un groupe méthylène, un groupe carbonyle ou un groupe de formule >C=N-OV

dans laquelle V représente : un atome d'hydrogène; un groupe alkylcarbonyle comportant de 2 à 6 atomes de carbone; un groupe arylcarbonyle dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe alkyle comportant de 1 à 5 atomes de carbone; ou un groupe alkyle substitué comportant de 1 à 5 atomes de carbone et substitué par au moins un des substituants (d) définis ci-dessous; et n est un entier de 1 à 3;

substituants (a):

groupes alkyle comportant de 1 à 5 atomes de carbone; groupes alcoxy comportant de 1 à 5 atomes de carbone; et atomes d'halogène;

substituants (b):

groupes aryle qui comportent de 6 à 10 atomes de carbone dans le noyau et qui sont non substitués ou substitués par au moins un des substituants (a) définis ci-dessus; groupes carboxy; groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone; et groupes de formule -CONR⁶R⁷, dans laquelle

R⁶ et R⁷ sont identiques ou différents, et chacun représente un atome d'hydrogène; un groupe alkyle comportant de 1 à 5 atomes de carbone; ou un groupe aryle comportant de 6 à 10 atomes de carbone dans le noyau et qui est non substitué ou substitué par au moins un des substituants (a) définis ci-dessus; ou R⁶ et R⁷, conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique qui comporte de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un hétéroatome supplémentaire d'azote et/ou d'oxygène et/ou de soufre, ledit groupe hétérocyclique étant non substitué ou substitué par au moins un des substituants (c) définis ci-dessous;

substituants (c):

groupes alkyle comportant de 1 à 5 atomes de carbone; et groupes aryle qui comportent de 6 à 10 atomes de carbone dans le noyau et qui sont non substitués ou substitués par au moins un des substituants (a) définis ci-dessus;

substituants (d):

groupes carboxy et groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone;

et ses sels pharmaceutiquement acceptables.

2. Composés selon la revendication 1, dans lesquels R¹ représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone.
3. Composés selon la revendication 1 ou la revendication 2, dans lesquels R² représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone.
4. Composés selon l'une quelconque des revendications 1 à 3, dans lesquels R³ et R⁴ sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 10 atomes de carbone; un groupe formyle; un groupe alkylcarbonyle comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone qui est non substitué ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un groupe carboxy; un groupe alcoxycarbonyle

comportant de 2 à 7 atomes de carbone; un groupe aryloxy-carbonyl comportant de 7 à 11 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant 2 à 11 atomes de carbone; un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone dont le groupement aryle est non substitué ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un atome d'halogène; ou un groupe alcoxy comportant de 1 à 5 atomes de carbone, qui est non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi :

- (1) les groupes aryle comportant 6 à 10 atomes de carbone qui sont eux-mêmes non substitués ou substitués par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène,
- (2) les groupes carboxy,
- (3) les groupes alcoxycarbonyl comportant de 2 à 6 atomes de carbone,
- (4) les groupes de formule $\text{-CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 sont identiques ou différents, et chacun représente

[1] un atome d'hydrogène,

[2] un groupe alkyle comportant de 1 à 5 atomes de carbone,

[3] un groupe aryle comportant de 6 à 10 atomes de carbone, qui est non substitué ou substitué par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène, ou

[4] R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'oxygène ou d'azote supplémentaire, le groupe étant non substitué ou substitué par au moins un substituant, le substituant étant choisi parmi les groupes alkyle comportant de 1 à 5 atomes de carbone et les groupes aryle comportant de 6 à 10 atomes de carbone, eux-mêmes étant non substitués ou substitués par 1 à 5 substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène.

5. Composés selon l'une quelconque des revendications 1 à 4, dans lesquels R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone.

6. Composés selon l'une quelconque des revendications 1 à 5, dans lesquels W représente un groupe méthylène, un groupe carbonyle ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène; un groupe alkylcarbonyl comportant de 2 à 6 atomes de carbone, un groupe arylcarbonyl comportant de 7 à 11 atomes de carbone ou un groupe alkyle comportant de 1 à 5 atomes de carbone, ledit groupe alkyle étant non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi:

les groupes carboxy et

les groupes alcoxycarbonyl comportant de 2 à 6 atomes de carbone.

7. Composés selon l'une quelconque des revendications 1 à 6, dans lesquels n vaut 1 ou 2.

8. Composés selon la revendication 1, dans lesquels:

R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone;

R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone;

R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 10 atomes de carbone; un groupe formyle; un groupe alkylcarbonyl comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyl comportant de 7 à 11 atomes de carbone qui est non substitué ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un groupe carboxy; un groupe alcoxycarbonyl comportant de 2 à 7 atomes de carbone; un groupe aryloxy-carbonyl comportant de 7 à 11 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone dont le groupement aryle est non substitué ou substitué par un à cinq substituants, les substituants étant choisis

parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un atome d'halogène; un groupe alcoxy comportant de 1 à 5 atomes de carbone, qui est non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi :

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(1) les groupes aryle comportant 6 à 10 atomes de carbone qui sont eux-mêmes non substitués ou substitués par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène,

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(2) les groupes carboxy,

(3) les groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone,

(4) les groupes de formule $-\text{CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 sont identiques ou différents, et chacun représente

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[1] un atome d'hydrogène,

[2] un groupe alkyle comportant de 1 à 5 atomes de carbone,

[3] un groupe aryle comportant de 6 à 10 atomes de carbone, qui est non substitué ou substitué par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène, ou

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[4] R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé qui comporte de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'oxygène ou d'azote supplémentaire, le groupe étant non substitué ou substitué par au moins un substituant, le substituant étant choisi parmi les groupes alkyle comportant de 1 à 5 atomes de carbone et les groupes aryle comportant de 6 à 10 atomes de carbone, eux-mêmes étant non substitués ou substitués par 1 à 5 substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène;

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R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone;

W représente un groupe méthylène, un groupe carbonyle ou un groupe de formule $>\text{C}=\text{N}-\text{OV}$ dans laquelle

V représente : un atome d'hydrogène, un groupe alkylcarbonyle comportant de 2 à 6 atomes de carbone, un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone ou un groupe alkyle comportant de 1 à 5 atomes de carbone, ledit groupe alkyle étant non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi:

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les groupes carboxy et

les groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone; et

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n vaut 1 ou 2.

9. Composés selon la revendication 1, dans lesquels R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone.

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10. Composés selon la revendication 1 ou la revendication 9, dans lesquels R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone.

11. Composés selon l'une quelconque des revendications 1, 9 et 10, dans lesquels R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 4 atomes de carbone; un groupe alkylcarbonyle comportant de 2 à 7 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué; un groupe carboxy; un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant de 2 à 7 atomes de carbone; un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué; un atome d'halogène; ou un groupe alcoxy comportant de 1 à 3 atomes de carbone, ledit groupe étant non substitué ou substitué par un ou deux substituants, les substituants étant choisis parmi :

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(1) les groupes aryle comportant 6 à 10 atomes de carbone et dont le groupement aryle est non substitué,

(2) les groupes carboxy,

- (3) les groupes alcoxycarbonyle comportant de 2 à 5 atomes de carbone,
 (4) les groupes carbamoyle, et
 (5) les groupes de formule $\text{-CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'oxygène ou d'azote supplémentaire, le groupe étant non substitué.
12. Composés selon l'une quelconque des revendications 1 et 9 à 11, dans lesquels R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone.
13. Composés selon l'une quelconque des revendications 1 et 9 à 12, dans lequel W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène, un groupe alkylcarbonyle comportant de 2 à 4 atomes de carbone ou un groupe benzoyle.
14. Composés selon la revendication 1, dans lesquels:
- R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone;
 R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone;
 R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 4 atomes de carbone; un groupe alkylcarbonyle comportant de 2 à 7 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone dont le groupement est non substitué; un groupe carboxy; un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant de 2 à 7 atomes de carbone un groupe aryloxy carbonyle comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué; un atome d'halogène; ou un groupe alcoxy comportant de 1 à 3 atomes de carbone, ledit groupe étant non substitué ou substitué par un à deux substituants, les substituants étant choisis parmi :
- (1) les groupes aryle comportant 6 à 10 atomes de carbone et dont le groupement aryle est non substitué,
 (2) les groupes carboxy,
 (3) les groupes alcoxycarbonyle comportant de 2 à 5 atomes de carbone,
 (4) les groupes carbamoyle, et
 (5) les groupes de formule $\text{-CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'oxygène supplémentaire ou d'azote, le groupe étant non substitué;
- R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone;
 W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène, un groupe alkylcarbonyle comportant de 2 à 4 atomes de carbone ou un groupe benzoyle; et n vaut 1 ou 2.
15. Composés selon la revendication 1, dans lesquels R^1 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.
16. Composés selon la revendication 1 ou la revendication 15, dans lesquels R^2 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.
17. Composés selon l'une quelconque des revendications 1, 15 et 16, dans lesquels R^3 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle, un groupe alkylcarbonyle comportant de 2 à 5 atomes de carbone, un groupe benzoyle, un groupe carboxy, un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone, un groupe hydroxy, un groupe alkylcarbonyloxy comportant de 2 à 5 atomes de carbone, un groupe benzoyloxy, méthoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-méthyléthoxy, carbamoylméthoxy, pipéridinocarbonylméthoxy ou morpholinocarbonylméthoxy, ou un atome de chlore ou de fluor.
18. Composés selon l'une quelconque des revendications 1 et 15 à 17, dans lesquels R^4 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, s-butyle ou t-butyle, un groupe alkylcarbonyle comportant de 2 à 5 atomes de carbone, un groupe benzoyle, un groupe hydroxy, un groupe alkylcarbo-

nyloxy comportant de 2 à 5 atomes de carbone, un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué, un groupe carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy ou 1-(t-butoxycarbonyl)-1-méthyléthoxy, ou un atome de chlore ou de fluor.

19. Composés selon l'une quelconque des revendications 1 et 15 à 18, dans lesquels R⁵ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.

20. Composés selon l'une quelconque des revendications 1 et 15 à 19, dans lesquels W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente un atome d'hydrogène ou un groupe acétyle.

21. Composés selon la revendication 1, dans lesquels :

R¹ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle; R² représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle; R³ représente un atome d'hydrogène, un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle, un groupe alkylcarbonyle comportant de 2 à 5 atomes de carbone, un groupe benzoyle, un groupe carboxy, un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone, un groupe hydroxy, un groupe alkylcarbonyloxy comportant de 2 à 5 atomes de carbone, un groupe benzoyloxy, méthoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-méthyléthoxy, carbamoylméthoxy, pipéridinocarbonylméthoxy ou morpholinocarbonylméthoxy, ou un atome de chlore ou de fluor;

R⁴ représente un atome d'hydrogène, un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, s-butyle ou t-butyle, un groupe alkylcarbonyle comportant de 2 à 5 atomes de carbone, un groupe benzoyle, un groupe hydroxy, un groupe alkylcarbonyloxy comportant de 2 à 5 atomes de carbone, un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué, un groupe carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy ou 1-(t-butoxycarbonyl)-1-méthyléthoxy, ou un atome de chlore ou de fluor;

R⁵ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle; W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente un atome d'hydrogène ou un groupe acétyle; et

n vaut 1 ou 2.

22. Composés selon la revendication 1, dans laquelle R¹ représente un groupe méthyle.

23. Composés selon la revendication 1 ou la revendication 22, dans lesquels R² représente un atome d'hydrogène ou un groupe méthyle.

24. Composés selon l'une quelconque des revendications 1, 22 et 23, dans lesquels R³ représente un atome d'hydrogène, un groupe méthyle, acétyle, carboxy, méthoxycarbonyl, éthoxycarbonyl, t-butoxycarbonyl, hydroxy, acétoxy, méthoxy, benzyloxy, carboxyméthoxy ou 3-carboxypropoxy, ou un atome de fluor.

25. Composés selon l'une quelconque des revendications 1 et 22 à 24, dans lesquels R⁴ représente un atome d'hydrogène, un groupe méthyle, t-butyle, acétyle, hydroxy, acétoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy ou 1-carboxy-1-méthyléthoxy, ou un atome de fluor.

26. Composés selon l'une quelconque des revendications 1 et 22 à 25, dans lesquels R⁵ représente un atome d'hydrogène ou un groupe méthyle.

27. Composés selon l'une quelconque des revendications 1 et 22 à 26, dans lesquels W représente un groupe méthylène.

28. Composés selon l'une quelconque des revendications 1 et 22 à 27, dans lesquels n est égal à 1.

29. Composés selon la revendication 1, dans lesquels :

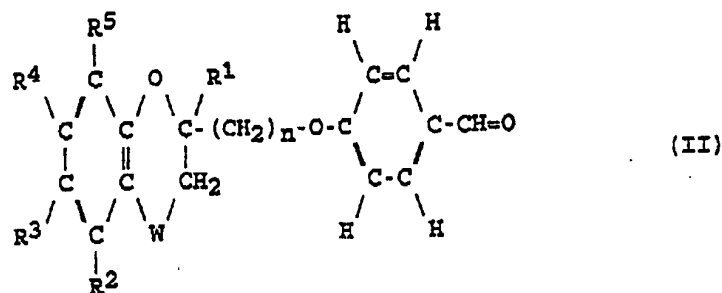
R¹ représente un groupe méthyle;
 R² représente un atome d'hydrogène ou un groupe méthyle;
 R³ représente un atome d'hydrogène, un groupe méthyle, acétyle, carboxy, méthoxycarbonyl, éthoxycarbonyl, t-butoxycarbonyl, hydroxy, acétoxy, méthoxy, benzyloxy, carboxyméthoxy ou 3-carboxypropoxy, ou un atome de fluor;
 R⁴ représente un atome d'hydrogène, un groupe méthyle, t-butyle, acétyle, hydroxy, acétoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy ou 1-carboxy-1-méthyléthoxy, ou un atome de fluor;
 R⁵ représente un atome d'hydrogène ou un groupe méthyle;
 W représente un groupe méthylène; et
 n et égal à 1.

30. 5-[4-(2-Méthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
31. 5-[4-(2,5,7-Triméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
32. 5-[4-(2,5,6,7,8-Pentaméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
33. 5-[4-(7-Hydroxy-2,8-diméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
34. 5-[4-(6-Hydroxy-2,5,7,8-tétraméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
35. 5-[4-(6-Acétoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
36. 5-[4-(6-Benzyloxy-2,5,7,8-tétraméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
37. 5-[4-(6-Carboxyméthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
38. 5-[4-[6-(3-Carboxypropoxy)-2,5,7,8-tétraméthylchromane-2-méthoxy]benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
39. 5-[4-[6-(1-Carboxy-1-méthyléthoxy)-2,5,7,8-tétraméthylchromane-2-méthoxy]benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
40. 5-[4-(6-Carbamoylméthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
41. 5-[4-[6-(Pipéridinocarbonyl)méthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy]benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
42. 5-[4-[6-(Morpholinocarbonyl)méthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy]benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
43. 5-[4-(6-Carboxy-2-méthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione, et ses sels pharmaceutiquement acceptables.
44. Composition pharmaceutique comprenant un composé de formule (I) ou un de ses sels pharmaceutiquement acceptables, selon l'une quelconque des revendications précédentes, en mélange avec un véhicule ou diluant pharmaceutiquement acceptable.
45. Composés de formule (I) et sels pharmaceutiquement acceptables de ces composés, selon l'une quelconque des

revendications 1 à 44, à utiliser en thérapeutique.

46. Utilisation de composés de formule (I) et de sels pharmaceutiquement acceptables de ces composés selon l'une quelconque des revendications 1 à 44, pour la fabrication d'un médicament permettant de réduire les taux de peroxyde lipidique chez un animal.

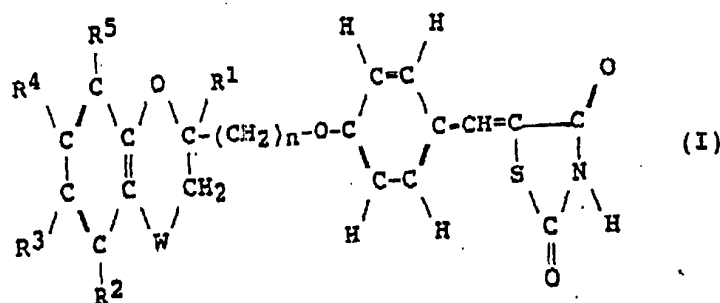
47. Procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 44, qui comprend : la réaction d'un composé de formule (II) :



(dans laquelle R¹, R², R³, R⁴, R⁵, n et W sont tels que définis dans la revendication 1) avec une thiazolidine-2,4-dione.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de formule (I)



[dans laquelle R¹, R² et R⁵ sont identiques ou différents, et chacun représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone; R³ et R⁴ sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 10 atomes de carbone; un groupe formyle; un groupe alkylcarbonyle comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyle dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe carboxy; un groupe alcoxycarbonyle comportant de 2 à 7 atomes de carbone; un groupe aryloxy carbonyle dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe hydroxy; un groupe alkyl- ou substitué par au moins un des substituants (a) définis ci-dessous; un groupe formyloxy; un groupe arylcarbonyloxy dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe alcoxy comportant de 1 à 5 atomes de carbone; un groupe alcoxy substitué comportant de 1 à 5 atomes de carbone et substitué par au moins un des substituants (b) définis ci-dessous; ou un atome d'halogène; W représente un groupe méthylène, un groupe carbonyle ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène; un groupe alkylcarbonyle comportant de 2 à 6 ato-

mes de carbone; un groupe arylcarbonyle dans lequel la partie aryle comporte de 6 à 10 atomes de carbone dans le noyau et est non substituée ou substituée par au moins un des substituants (a) définis ci-dessous; un groupe alkyle comportant de 1 à 5 atomes de carbone; ou un groupe alkyle substitué comportant de 1 à 5 atomes de carbone et substitué par au moins un des substituants (d) définis ci-dessous; et

n est un entier de 1 à 3;

substituants (a):

groupes alkyle comportant de 1 à 5 atomes de carbone; groupes alcoxy comportant de 1 à 5 atomes de carbone; et atomes d'halogène;

substituants (b):

groupes aryle qui comportent de 6 à 10 atomes de carbone dans le noyau et qui sont non substitués ou substitués par au moins un des substituants (a) définis ci-dessus; groupes carboxy; groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone; et groupes de formule $-\text{CONR}^6\text{R}^7$, dans laquelle

R^6 et R^7 sont identiques ou différents, et chacun représente un atome d'hydrogène; un groupe alkyle comportant de 1 à 5 atomes de carbone; ou un groupe aryle comportant de 6 à 10 atomes de carbone dans le noyau et qui est non substitué ou substitué par au moins un des substituants (a) définis ci-dessus; ou R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique qui comporte de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un hétéroatome supplémentaire d'azote et/ou d'oxygène et/ou de soufre, ledit groupe hétérocyclique étant non substitué ou substitué par au moins un des substituants (c) définis ci-dessous;

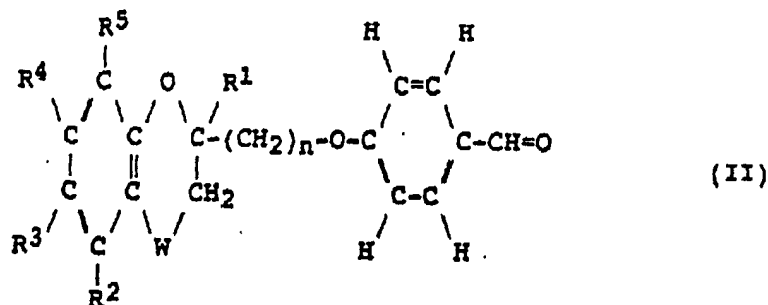
substituants (c):

groupes alkyle comportant de 1 à 5 atomes de carbone; et groupes aryle qui comportent de 6 à 10 atomes de carbone dans le noyau et qui sont non substitués ou substitués par au moins un des substituants (a) définis ci-dessus;

substituants (d):

groupes carboxy et groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone;]

et de ses sels, ce procédé comprenant la réaction d'un composé de formule (II) :



(dans laquelle R^1 , R^2 , R^3 , R^4 , R^5 , n et W sont tels que définis ci-dessus) avec une thiazolidine-2,4-dione.

2. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone.
3. Procédé selon la revendication 1 ou la revendication 2, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone.
4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 10 atomes de carbone; un groupe formyle; un groupe alcoxycarbonyle comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone qui est non substitué ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un groupe carboxy; un groupe

alcoxycarbonyle comportant de 2 à 7 atomes de carbone; un groupe aryloxy carbonyle comportant de 7 à 11 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant 2 à 11 atomes de carbone; un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone dont le groupement aryle est non substitué ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un atome d'halogène; ou un groupe alcoxy comportant de 1 à 5 atomes de carbone, qui est non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi :

- (1) les groupes aryle comportant 6 à 10 atomes de carbone qui sont eux-mêmes non substitués ou substitués par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène,
- (2) les groupes carboxy,
- (3) les groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone,
- (4) les groupes de formule $\text{-CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 sont identiques ou différents, et chacun représente

- [1] un atome d'hydrogène,
- [2] un groupe alkyle comportant de 1 à 5 atomes de carbone,
- [3] un groupe aryle comportant de 6 à 10 atomes de carbone, qui est non substitué ou substitué par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène, ou
- [4] R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'azote ou d'oxygène supplémentaire, le groupe étant non substitué ou substitué par au moins un substituant, le substituant étant choisi parmi les groupes alkyle comportant de 1 à 5 atomes de carbone et les groupes aryle comportant de 6 à 10 atomes de carbone, eux-mêmes étant non substitués ou substitués par 1 à 5 substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel W représente un groupe méthylène, un groupe carbonyle ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène; un groupe alkylcarbonyle comportant de 2 à 6 atomes de carbone, un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone ou un groupe alkyle comportant de 1 à 5 atomes de carbone, ledit groupe alkyle étant non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi:

les groupes carboxy et
les groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel n vaut 1 ou 2.

8. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel :

R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone;
 R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone;
 R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 10 atomes de carbone; un groupe formyle; un groupe alkylcarbonyle comportant de 2 à 11 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone qui est non substitué

ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un groupe aryloxy-carboxy; un groupe alcoxycarbonyle comportant de 2 à 7 atomes de carbone; un groupe arylalcoxy-carbonyle comportant de 7 à 11 atomes de carbone; un groupe hydroxy; un groupe alkylalcoxy-carbonyle comportant de 7 à 11 atomes de carbone dont le groupement aryle est non substitué ou substitué par un à cinq substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène; un groupe d'halogène; ou un groupe alcoxy comportant de 1 à 5 atomes de carbone, qui est non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi :

- (1) les groupes aryle comportant 6 à 10 atomes de carbone qui sont eux-mêmes non substitués ou substitués par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène,
- (2) les groupes carboxy,
- (3) les groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone,
- (4) les groupes de formule $-\text{CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 sont identiques ou différents, et chacun représente

- [1] un atome d'hydrogène,
- [2] un groupe alkyle comportant de 1 à 5 atomes de carbone,
- [3] un groupe aryle comportant de 6 à 10 atomes de carbone, qui est non substitué ou substitué par un à cinq substituants sur le noyau aromatique, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène, ou
- [4] R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un hétéroatome d'oxygène ou d'azote supplémentaire, le groupe étant non substitué ou substitué par au moins un substituant, le substituant étant choisi parmi les groupes alkyle comportant de 1 à 5 atomes de carbone et les groupes aryle comportant de 6 à 10 atomes de carbone, eux-mêmes étant non substitués ou substitués par 1 à 5 substituants, les substituants étant choisis parmi les groupes alkyle comportant de 1 à 5 atomes de carbone, les groupes alcoxy comportant de 1 à 5 atomes de carbone et les atomes d'halogène;

R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 10 atomes de carbone; W représente un groupe méthylène, un groupe carbonyle ou un groupe de formule $>\text{C}=\text{N}-\text{OV}$ dans laquelle V représente : un atome d'hydrogène, un groupe alkylalcoxy-carbonyle comportant de 2 à 6 atomes de carbone, un groupe arylalcoxy-carbonyle comportant de 7 à 11 atomes de carbone ou un groupe alkyle comportant de 1 à 5 atomes de carbone, ledit groupe alkyle étant non substitué ou substitué par un à trois substituants, les substituants étant choisis parmi :

les groupes carboxy et
les groupes alcoxycarbonyle comportant de 2 à 6 atomes de carbone; et

n vaut 1 ou 2.

9. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone.
10. Procédé selon la revendication 1 ou la revendication 9, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone.
11. Procédé selon l'une quelconque des revendications 1, 9 et 10, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant

de 1 à 4 atomes de carbone; un groupe alkylcarbonyle comportant de 2 à 7 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué; un groupe carboxy; un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant de 2 à 7 atomes de carbone; un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué; un atome d'halogène; ou un groupe alcoxy comportant de 1 à 3 atomes de carbone, ledit groupe étant non substitué ou substitué par un ou deux substituants, les substituants étant choisis parmi :

- (1) les groupes aryle comportant 6 à 10 atomes de carbone et dont le groupement aryle est non substitué,
- (2) les groupes carboxy,
- (3) les groupes alcoxycarbonyle comportant de 2 à 5 atomes de carbone,
- (4) les groupes carbamoyle, et
- (5) les groupes de formule $\text{-CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'oxygène ou d'azote supplémentaire, le groupe étant non substitué.

12. Procédé selon l'une quelconque des revendications 1 et 9 à 11, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone.

13. Procédé selon l'une quelconque des revendications 1 et 9 à 12, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène, un groupe alkylcarbonyle comportant de 2 à 4 atomes de carbone ou un groupe benzoyle.

14. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel :

R^1 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone;
 R^2 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone;
 R^3 et R^4 sont identiques ou différents, et chacun représente : un atome d'hydrogène; un groupe alkyle comportant de 1 à 4 atomes de carbone; un groupe alkylcarbonyle comportant de 2 à 7 atomes de carbone; un groupe arylcarbonyle comportant de 7 à 11 atomes de carbone dont le groupement est non substitué; un groupe carboxy; un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone; un groupe hydroxy; un groupe alkylcarbonyloxy comportant de 2 à 7 atomes de carbone un groupe aryloxycarbonyle comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué; un atome d'halogène; ou un groupe alcoxy comportant de 1 à 3 atomes de carbone, ledit groupe étant non substitué ou substitué par un à deux substituants, les substituants étant choisis parmi :

- (1) les groupes aryle comportant 6 à 10 atomes de carbone et dont le groupement aryle est non substitué,
- (2) les groupes carboxy,
- (3) les groupes alcoxycarbonyle comportant de 2 à 5 atomes de carbone,
- (4) les groupes carbamoyle, et
- (5) les groupes de formule $\text{-CONR}^6\text{R}^7$, dans laquelle R^6 et R^7 , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe hétérocyclique saturé comportant de 3 à 7 atomes dans le noyau, dont 1 est ledit atome d'azote et 0 ou 1 est un atome d'oxygène ou d'azote supplémentaire, le groupe étant non substitué;

R^5 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone;
W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente : un atome d'hydrogène, un groupe alkylcarbonyle comportant de 2 à 4 atomes de carbone ou un groupe benzoyle; et n vaut 1 ou 2.

15. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R^1 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.

16. Procédé selon la revendication 1 ou la revendication 15, dans lequel les réactifs et les conditions réactionnelles

sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R² représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.

- 5 17. Procédé selon l'une quelconque des revendications 1, 15 et 16, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R³ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle, un groupe alkylcarbonyle comportant 2 à 5 atomes de carbone, un groupe benzoyle, un groupe carboxy, un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone, un groupe hydroxy, un groupe alkylcarbonyloxy comportant de 2 à 5 atomes de carbone, un groupe benzoyloxy, méthoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-méthyléthoxy, carbamoylméthoxy, pipéridinocarbonylméthoxy ou morpholinocarbonylméthoxy, ou un atome de chlore ou de fluor.
- 10 18. Procédé selon l'une quelconque des revendications 1 et 15 à 17, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R⁴ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, s-butyle ou t-butyle, un groupe alkylcarbonyle comportant 2 à 5 atomes de carbone, un groupe benzoyle, un groupe hydroxy, un groupe alkylcarbonyloxy comportant de 2 à 5 atomes de carbone, un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué, un groupe carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy ou 1-(t-butoxycarbonyl)-1-méthyléthoxy, ou un atome de chlore ou de fluor.
- 15 19. Procédé selon l'une quelconque des revendications 1 et 15 à 18, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R⁵ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.
- 20 20. Procédé selon l'une quelconque des revendications 1 et 15 à 19, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente un atome d'hydrogène ou un groupe acétyle.
- 25 21. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel:

35 R¹ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle; R² représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle; R³ représente un atome d'hydrogène, un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle, un groupe alkylcarbonyle comportant de 2 à 5 atomes de carbone, un groupe benzoyle, un groupe carboxy, un groupe alcoxycarbonyle comportant de 2 à 5 atomes de carbone, 3-carboxypropoxy, un groupe benzoyloxy, méthoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy, 1-(t-butoxycarbonyl)-1-méthyléthoxy, carbamoylméthoxy, pipéridinocarbonylméthoxy ou morpholinocarbonylméthoxy, ou un atome de chlore ou de fluor;

40 R⁴ représente un atome d'hydrogène, un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, s-butyle ou t-butyle, un groupe alkylcarbonyle comportant de 2 à 5 atomes de carbone, un groupe benzoyle, un groupe hydroxy, un groupe alkylcarbonyloxy comportant de 2 à 5 atomes de carbone, un groupe arylcarbonyloxy comportant de 7 à 11 atomes de carbone et dont le groupement aryle est non substitué, un groupe carboxyméthoxy, 1-carboxy-1-méthyléthoxy, méthoxycarbonylméthoxy, 3-méthoxycarbonylpropoxy, 1-méthoxycarbonyl-1-méthyléthoxy, t-butoxycarbonylméthoxy, 3-(t-butoxycarbonyl)propoxy ou 1-(t-butoxycarbonyl)-1-méthyléthoxy, ou un atome de chlore ou de fluor;

45 R⁵ représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle; W représente un groupe méthylène ou un groupe de formule >C=N-OV dans laquelle V représente un atome d'hydrogène ou un groupe acétyle; et

50 n vaut 1 ou 2.
- 55 22. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R¹ représente un groupe méthyle.

23. Procédé selon la revendication 1 ou la revendication 22, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R² représente un atome d'hydrogène ou un groupe méthyle.

5 24. Procédé selon l'une quelconque des revendications 1, 22 et 23, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R³ représente un atome d'hydrogène, un groupe méthyle, acétyle, carboxy, méthoxycarbonyle, éthoxycarbonyle, t-butoxycarbonyle, hydroxy, acétoxy, méthoxy, benzyloxy, carboxyméthoxy ou 3-carboxypropoxy, ou un atome de fluor.

10 25. Procédé selon l'une quelconque des revendications 1 et 22 à 24, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R⁴ représente un atome d'hydrogène, un groupe méthyle, t-butyle, acétyle, hydroxy, acétoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy ou 1-carboxy-1-méthyléthoxy, ou un atome de fluor.

15 26. Procédé selon l'une quelconque des revendications 1 et 22 à 25, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel R⁵ représente un atome d'hydrogène ou un groupe méthyle.

20 27. Procédé selon l'une quelconque des revendications 1 et 22 à 26, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel W représente un groupe méthylène.

25 28. Procédé selon l'une quelconque des revendications 1 et 22 à 27, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel n est égal à 1.

29. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisies de manière à préparer un composé de formule (I), ou un de ses sels ou esters, dans lequel:

30 R¹ représente un groupe méthyle;
R² représente un atome d'hydrogène ou un groupe méthyle;
R³ représente un atome d'hydrogène ou un groupe méthyle, acétyle, carboxy, méthoxycarbonyle, éthoxycarbonyle, t-butoxycarbonyle, hydroxy, acétoxy, méthoxy, benzyloxy, carboxyméthoxy ou 3-carboxypropoxy, ou un atome de fluor;
35 R⁴ représente un atome d'hydrogène, un groupe méthyle, t-butyle, acétyle, hydroxy, acétoxy, benzyloxy, carboxyméthoxy, 3-carboxypropoxy ou 1-carboxy-1-méthyléthoxy, ou un atome de fluor;
R⁵ représente un atome d'hydrogène ou un groupe méthyle;
W représente un groupe méthylène; et
40 n est égal à 1.

30. Procédé selon la revendication 1, dans lequel les réactifs et les conditions réactionnelles sont choisis de manière à préparer:

45 la 5-[4-(2-méthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(2,5,7-triméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(2,5,6,7,8-pentaméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(7-hydroxy-2,8-diméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(6-hydroxy-2,5,7,8-tétraméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione;
50 la 5-[4-(6-acétoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione;
la 5-[4-(6-benzyloxy-2,5,7,8-tétraméthylchromane-2-méthoxy)-benzylidène]-2,4-thiazolidinedione;
la 5-[4-(6-carboxyméthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(6-(3-carboxypropoxy)-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
55 la 5-[4-(6-(1-carboxy-1-méthyléthoxy)-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(6-carbamoylméthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;
la 5-[4-(6-(pipéridinocarbonyl)méthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;

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la 5-[4-{6-(morpholinocarbonyl)méthoxy-2,5,7,8-tétraméthylchromane-2-méthoxy}benzylidène]-2,4-thiazolidinedione;

la 5-[4-(6-carboxy-2-méthylchromane-2-méthoxy)benzylidène]-2,4-thiazolidinedione;

- 5 **31.** Procédé de préparation d'une composition pharmaceutique comprenant le mélange d'un composé de formule (I) ou d'un de ses sels pharmaceutiquement acceptables avec un véhicule ou diluant pharmaceutiquement acceptable.
- 10 **32.** Utilisation de composés de formule (I) et de sels pharmaceutiquement acceptables de ces composés, tels que définis dans l'une quelconque des revendications 1 à 30, pour la fabrication d'un médicament destiné à réduire les taux de peroxyde lipidique chez un animal.

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